BioCentury
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# SHORTER AND FATTER

BY STEVE USDIN, WASHINGTON EDITOR

The House Energy & Commerce Committee's 21st Century Cures draft legislation got 200 pages shorter and $10 billion more expensive last week as Republicans dropped controversial provisions and added NIH funding to gain support from Democrats.

The second iteration of the legislative discussion draft remains very much a work in progress with large portions bracketed, meaning the language is tentative, and with several placeholders indicating areas where there isn't sufficient agreement to propose even bracketed text.

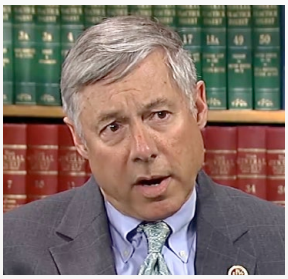
As expected, scores of provisions in the first draft that FDA considered unachievable or otherwise opposed have been either dropped or reworked to make them acceptable to the agency.

The ax also fell on every proposal to provide new market exclusivity as an incentive for drug development, though it is likely that some will be revived in forms that are more specifically targeted at achieving clear public policy goals, and less generous to drug companies.

New provisions, if retained in the final legislation, could increase the speed and reduce the cost of developing targeted therapies. These include language allowing FDA to approve supplemental indications based on real world and other clinical evidence rather than controlled trials, and provisions making it possible for the agency to approve a drug for an Orphan condition based on evidence of safety and efficacy of a different drug that has the same mechanism of action.

New proposals in the draft that would allow FDA to pay higher salaries could help the agency recruit and retain qualified employees.

The draft also seeks to slightly loosen existing restrictions on drug company communications with payers and formulary committees about pharmacoeconomics.



# "WITH RESPECT TO DIAGNOSTICS, WE REMAIN ABSOLUTELY COMMITTED TO DEVELOPING A MODERNIZED REGULATORY FRAMEWORK."

## REP. FRED UPTON

Republicans and Democrats are continuing to work on proposals that could be added to the bill, if they gain bipartisan support. Republicans said at an April 30 Senate hearing that they haven't given up on trying to reform regulation of diagnostics. But it will be extremely difficult to gain consensus on issues like FDA oversight of laboratory-developed tests (LDTs) and direct-to-consumer genomics tests.

Democrats said they will try to make the legislation do more to advance the development of targeted therapies for children, a goal senior FDA officials publicly support.

E&C Committee Chairman Fred Upton (R-Mich.) has not announced a timetable for moving from discussion drafts to legislation, but he made it clear last week that he will set an aggressive schedule.

### CUTTING ROOM FLOOR

The most dramatic changes between the first and second versions of the discussion draft are in sections that would have changed the way FDA operates.

Scores of provisions that sought to require specific actions on tight timetables were left on the cutting room floor or modified so they have little or no effect.

The January draft sought to create a pathway for biomarker qualification that FDA staff complained could have created a deluge of applications that they would have had to review on unrealistically short deadlines. Implementing the pathway would have brought drug review activities to a standstill, Janet Woodcock, director of FDA's Center for Drug Evaluation and Research (CDER) told E&C members.

All of the deadlines from the first draft for reviewing and acting on biomarker qualification applications have disappeared. Version 2.0 requires that FDA establish a process for qualification of biomarkers and other drug development tools, but leaves it up to the agency to design the process.

Woodcock said the new "draft codifies process we have in place" to qualify biomarkers.

Some sections of the January draft that would have lowered approval standards or limited FDA's ability to request or examine data have been dropped or reworded.

For example, FDA officials were outraged by language in the first draft that sought to force the agency to make certain device review decisions based on peer-reviewed journal articles and barred it from requesting the underlying data. The new draft gives FDA discretion to accept peer-reviewed journal articles, and allows it to request the underlying data.

Although there are far fewer new mandates for FDA in the new draft, it includes requirements for the agency to create several new programs, write over a dozen new guidance documents, and implement new policies. And it still doesn't provide any new funding.

Woodcock warned the E&C Committee that imposing new burdens in the absence of resources could cause FDA to slow drug review activities.

When limited resources force FDA to choose between statutory requirements and PDUFA goals, "there is no doubt that statutory instructions will come first," she said.

Republicans and Democrats said at last week's hearing that they recognize the problem and will seek additional funding for FDA. If they are unable to secure funding, it is possible that many of the FDA provisions in the 21st Century Cures draft could be shifted to PDUFA reauthorization legislation.

### EXCLUDED, FOR NOW

There were so many provisions in the January draft seeking to use additional market exclusivity as an incentive for drug development, and the legislative language was so loose, that most new drugs and many older drugs would have been eligible for some form of additional exclusivity.

Democrats are deeply skeptical about the exclusivity provisions, viewing them as giveaways to the pharmaceutical industry.

At last week's hearing, Rep. Jan Schakowsky (D-Ill.) said, "added exclusivity is not needed to bring new cures to patients." Instead, she urged her colleagues to take steps to reduce the cost of drugs, including by giving HHS the right to negotiate prices paid by Medicare's Part D program.

The word "exclusivity" is not used a single time in the new draft. Entire sections of the January draft have been vaporized, including those that used exclusivity as an incentive to repurpose drugs for Orphan indications and to revive so-called "dormant" drugs that have little or no patent life.

The idea of creating incentives for developing dormant therapies and to repurpose drugs is not dead. The new draft contains a placeholder for "repurposing drugs for serious and life-threatening diseases and conditions," and members from both parties said at last week's hearing that they are working on new language.

"I have said all along that broadly extending drug exclusivity will not solve the problems 21st Century Cures sets out to address," said Rep. Frank Pallone (D-N.J.), the ranking Democrat on the committee.

However, Pallone added, "We are going to continue discussions on how we can incentivize development of a narrow class of drugs that have been abandoned because of inadequate remaining patent life."

"If such drugs fill an unmet medical need for treating a serious or life-threatening disease," Pallone said, "it may be appropriate to provide companies with limited additional exclusivity for companies to spend the resources needed to determine if they work. I appreciate the chairman's commitment to me to continue to discuss this policy and ensure that it is targeted only to where it is needed."

Upton said the final bill will "include incentives for doing research on drugs that are FDA-approved but can be repurposed to help patients with different types of illnesses."

### NEW PROVISIONS

In addition to hitting the delete key a lot, E&C staff used the insert function to introduce a few ideas that could increase the speed and reduce the cost of developing targeted therapies.

One of the insertions is a section on "utilizing evidence from clinical experience" that cautiously moves FDA in the direction of approving new indications and allowing sponsors to meet postapproval study commitments based on data from sources other than randomized clinical trials, such as observational trials and registries.

The agency would be required to commission a public-private entity or independent research organization to help it develop a framework for using clinical experience, undertake a public stakeholder consultation process and issue guidance.

In parallel, FDA would design and execute pilot demonstrations testing the use of the Sentinel postmarket safety surveillance system to collect clinical experience data.

The clinical evidence provisions are a substantial departure from current law, which stipulates that approvals must be supported by "adequate and well-controlled studies." Patient groups and drug companies, however, may be disappointed by the lack of deadlines, and by procedural steps that could take years to implement.

Another insertion filled in a placeholder in the January draft for a section on FDA regulation of precision medicine. The draft defines a precision medicine drug as one that addresses the underlying cause of disease in a defined patient population.

The new language allows FDA to approve a precision drug for an Orphan indication based on "data or information previously developed by the sponsor of a prior approved drug or indication (or another sponsor that has provided the sponsor with a contractual right of reference to such data and information)." The new drug must act through "the same or similar precision medicine approach as that of the prior approved drug or indication."

The draft doesn't explain what this section is intended to accomplish. It could be designed to facilitate the development of drugs for rare conditions that have no available treatments.

## AN INNOVATIVE FUND

The 21st Century Cures discussion draft released last week sidesteps standard congressional appropriations procedures to allocate $2 billion per year for five years to an NIH "Innovation Fund."

Allocation of taxpayer money is usually a two-step process, starting with a congressional committee "authorizing" — which really means suggesting — that a certain amount of money be spent for a specific purpose. Appropriations committees in the House of Representatives and Senate then decide how much, if any, will actually be appropriated.

The fate of the Cures Acceleration Network (CAN) illustrates the stark difference between authorizing and appropriating.

The Affordable Care Act established CAN to fund a massive NIH translational research effort. The law authorized $500 million for 2010 and "such sums as may be necessary" for subsequent years. In practice, CAN has limped along on $10-$20 million per year.

To make certain NIH actually receives $10 billion for the Innovation Fund, the draft bill states that the money is both authorized and appropriated. Because the funding would not go through the usual appropriations process, it will take consent of — and creative thinking by — congressional leadership to make it happen.

"One of the things I am most proud of is the money for NIH," House Energy & Commerce Committee Chairman Fred Upton (R-Mich.) said at an April 30 hearing. He did not say where the money is going to come from, nor did any of the other committee members.

It is likely that E&C will be required to cut $10 billion from other programs under its jurisdiction.

The draft states that the fund is to be used for precision medicine and young emerging scientists initiatives, and for other uses. It indicates that definitions of the two initiatives, and parameters for other uses, are "to be supplied."

Based on past practices, if the fund is created, NIH and its grantees are likely to apply a great deal of creativity to the way precision medicine is defined.

— STEVE USDIN

Committee staff had drafted language creating a seven-year exclusivity period for precision drugs, similar to Orphan exclusivity, but the exclusivity provision didn't make it into the draft.

A third insertion in the current draft attempts to help FDA solve one of its most vexing problems, the recruitment and retention of highly qualified scientific and medical personnel.

At the hearing, Woodcock said many of her employees could double their salaries by taking jobs in the private sector, and that CDER is having a "desperate time" recruiting neurologists and other specialists.

> "I HAVE SAID ALL ALONG THAT BROADLY EXTENDING DRUG EXCLUSIVITY WILL NOT SOLVE THE PROBLEMS 21ST CENTURY CURES SETS OUT TO ADDRESS."
>
> REP. FRANK PALLONE

The draft bill expands the Silvio O. Conte Senior Biomedical Research Service, a mechanism Congress created in 1991 to allow HHS to pay scientists salaries similar to those they could receive in the private sector. If the draft is enacted, the cap on the number of Biomedical Research Service members, currently 500, would be eliminated.

The maximum salary for service members, currently about $200,000 per year, would be increased to the president's salary, currently $400,000 per year.

### CODIFYING PRACTICE

Another new section in the recent draft allows FDA to streamline approval decisions for supplemental indications by allowing it to review data summaries rather than detailed data sets. Like many provisions in the draft related to FDA procedures, this proposal would codify existing or emerging practices.

The Office of Hematology and Oncology Products in CDER is already experimenting with approvals of supplemental indications based on summary data, its director, Richard Pazdur, told BioCentury TV in a recent interview.

The process is intended to speed reviews when FDA already has a lot of data about safety and efficacy in related indications. For example, in August 2014, FDA approved Avastin bevacizumab from Roche's Genentech Inc. unit for cervical cancer based on summary data.

"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, not looking through each line of the data, but looking at summary tables and really trying to expedite the approval, because we do have confidence in the safety of the drug," Pazdur said.

He added that the streamlined process is for products that have a "vast amount" of prior experience. "In other words, 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 from the one that was approved," Pazdur said.

### MORE TO COME

In addition to repurposing incentives, E&C members said at last week's hearing that as the bill works its way through the legislative process they intend to add provisions on diagnostics, pediatric R&D, telemedicine, and other areas.

"With respect to diagnostics, we remain absolutely committed to developing a modernized regulatory framework for these innovative and increasingly important tests and services," Upton said. He said he hopes to hold a legislative hearing on regulating diagnostics in July.

Jeffrey Shuren, director of FDA's Center for Devices and Radiological Health (CDRH), expressed the hope to the committee that final legislation "will have the support of the labs, the device industry, all of you, and the FDA as well."

Shuren didn't give any indication of how this consensus, which has been elusive, could be achieved.

Rep. G. K. Butterfield (D-N.C.) said he plans to work with other members to include language in the final legislation to make permanent the rare disease Priority Review voucher program created as a pilot by the Creating Hope Act. The last voucher will be issued in less than a year if the law is not renewed.

At the end of last week's hearing, Rep. Diana DeGette (D-Colo.) asked FDA and NIH witnesses, "what else we should consider that is not in this discussion draft?"

Woodcock replied that she is concerned that children with cancer "are currently being left out of the targeted therapy revolution."

The Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act require sponsors of drugs for adult indications to study pediatric indications if a disease occurs in children. But the problem, according to Woodcock and pediatric cancer advocates, is that cancers are defined by tissue of origin, such as prostate or breast cancer, rather than by molecular pathway.

Prostate and breast cancers, as an example, do not occur in children. Yet the molecular targets of prostate and breast cancer drugs could be important for pediatric cancers.

DeGette said the E&C Committee has discussed and failed to come to consensus on measures to improve pediatric cancer drug development. She and other members said they will continue to try to add pediatric cancer language.

### QOL AT NIH

NIH Director Francis Collins and other senior NIH staff devoted enormous amounts of time to the 21st Century Cures process, and they received a substantial return on the investment.

E&C Committee Republicans are trying to meet the Democrats' demands for increased NIH funding by using an unusual legislative maneuver to

bypass the appropriations process and funnel $2 billion per year for five years into an NIH "Innovation Fund" (see "An Innovative Fund," page 3).

In addition, the draft bill includes a number of items from NIH's wish list, and it makes no effort to fundamentally change the way the institutes operate.

NIH sought and received a waiver from the Paperwork Reduction Act which, contrary to its name, imposes substantial administrative requirements on NIH employees and grantees.

NIH also received support for its contention that HHS should ease travel restrictions that severely limit the ability of its scientists to attend scientific meetings. The draft includes a statement that it is the "sense of Congress that participation in or sponsorship of scientific conferences and meetings is essential to the mission of the National Institutes of Health."

The draft contains similar language for FDA.

The draft also seeks to lift a restriction that NIH feels is hindering its efforts to advance translational medicine.

When the National Center for Advancing Translational Science (NCATS) was created, there was concern from industry and the scientific community that NIH was creating a government-owned drug company that would compete with the private sector. To prevent this, Congress barred NCATS from funding or conducting studies beyond Phase IIb.

The draft lifts the prohibition, allowing NCATS to fund and conduct Phase III studies.

It also gives NIH the power to require that investigators share scientific data generated from NIH grants.

The bill is intended to increase "accountability" of NIH, largely by giving the NIH director, a political appointee, more power.

It creates a five-year term for institute and center directors, and gives the NIH director discretion to renew a director or appoint a replacement. It does not establish criteria for removing a director or failing to renew a director. bc

## COMPANIES AND INSTITUTIONS MENTIONED

**Genentech Inc.**, South San Francisco, Calif.
**National Institutes of Health** (NIH), Bethesda, Md.
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
**U.S. Food and Drug Administration** (FDA), Silver Spring, Md.

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EMERGING COMPANY PROFILE

# NIXING NIEMANN-PICK

BY JENNIFER RHODES, STAFF WRITER

Vtesse Inc. is hoping to change the course of disease in Niemann-Pick type C, a fatal ultra-Orphan lysosomal storage disorder, using a compound plucked from NIH's Therapeutics for Rare and Neglected Diseases repurposing project.

Niemann-Pick type C is caused by the progressive accumulation of unesterified cholesterol and glycosphingolipids in the CNS and visceral organs. The accumulation stems from mutations in the Niemann-Pick disease type C1 (NPC1) or NPC2 genes, which encode proteins involved in the intracellular trafficking of cholesterol and other lipids.

NPC patients typically exhibit ataxia, swallowing problems, seizures and progressive impairment of motor and intellectual function. Average life expectancy is 15-20 years.

Vtesse's VTS-270 is a formulation of cyclodextrin that binds to and removes cholesterol. In animal models, it has slowed disease progression and prolonged survival vs. Zavesca miglustat, the only approved therapy for the indication.

Cyclodextrins are used as excipients in over 30 marketed drugs; however, researchers began investigating the class for lysosomal storage disorders because they also form complexes with cholesterol.

Cyclodextrin transports cholesterol independent of the NPC proteins, although Vtesse President and CEO Ben Machielse said its exact mechanism is not known.

The process may involve lysosomal exocytosis, according to NIH, which in 2010 selected 2-hydroxypropyl-b-cyclodextrin for NPC under the Therapeutics for Rare and Neglected Diseases (TRND) project.

Vtesse has an exclusive, worldwide license from NIH to develop the compound, which it dubbed VTS-270, for lysosomal storage disorders.

In a mouse model of the disorder, researchers from Albert Einstein College of Medicine and colleagues showed 2-hydroxypropyl-b-cyclodextrin nearly doubled the median life span compared with Zavesca, while the addition of Zavesca to VTS-270 did not improve life span vs. VTS-270 alone. Data were in a poster at the Lysosomal Disease Network World Symposium in February.

**VTESSE INC.**
Gaithersburg, Md.

**Technology:** 2-hydroxypropyl-b-cyclodextrin

**Disease focus:** Endocrine/Metabolic

**Clinical status:** Phase I

**Founded:** 2014 by Ben Machielse and Ravi Venkataramani

**University collaborators:** NIH, University of Pennsylvania, Washington University and Albert Einstein College of Medicine

**Corporate partners:** None

**Number of employees:** 6

**Funds raised:** $25 million

**Investors:** New Enterprise Associates, Pfizer Venture Investments, Lundbeckfond Ventures, Bay City Capital and Alexandria Venture Investments

**CEO:** Ben Machielse

**Patents:** 8 issued covering use of hydroxypropyl-b-cyclodextrin alone and in combination with delta-tocopherol and its derivatives to treat lysosomal storage diseases

Also that month, University of Pennsylvania researchers published data in *Science Translational Medicine* showing VTS-270 slowed disease progression and significantly prolonged survival in a cat model of NPC1.

Zavesca from Actelion Ltd. and UCB Group is a glucosylceramide synthase inhibitor that slows disease progression. The drug is approved for NPC in at least 40 countries, but it does not reduce cholesterol and has GI tolerability issues.

According to NIH, a "controlled study and a series of case reports suggest limited efficacy for miglustat" in NPC. There are no NPC survival data on Zavesca's European label.

FDA issued a complete response letter for the drug in the indication in 2010 and asked for additional preclinical and clinical information. Actelion declined to comment on U.S. plans for Zavesca for NPC.

At least one other compound is in the clinic for NPC. Orphazyme ApS plans to start a Phase II/III trial in June of arimoclomol, a small molecule inducer of the heat shock response.

CEO Anders Hinsby said preclinical studies have focused on motor coordination and activity, but said Orphazyme has "observed significant survival benefit." A manuscript with the data is under review by a scientific journal.

Machielse declined to comment on arimoclomol.

NIH is evaluating VTS-270 in a Phase I trial. Next half, Vtesse plans to start a pivotal, sham-controlled Phase II/III trial to evaluate twice-monthly intrathecal injections in about 50 patients. Vtesse has runway to complete the Phase II/III trial, Machielse said.

Machielse noted Vtesse has access to data from an NIH natural history study for NPC, which he said will help the company power the study and design the clinical development program. Vtesse also has been working with more than half a dozen NPC patient groups and incorporating patient feedback.

VTS-270 has FDA and EMA Orphan Drug designation for NPC.

The biotech also has an exclusive license from NIH for delta-tocopherol and for other derivatives of tocopherol to treat NPC and other lysosomal storage disorders.

The company is the first spinout of Orphan drug accelerator Cydan Development Inc. bc

## COMPANIES AND INSTITUTIONS MENTIONED

**Actelion Ltd.** (SIX:ATLN), Allschwil, Switzerland

**Albert Einstein College of Medicine of Yeshiva University**, New York, N.Y.

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

**Cydan Development Inc.**, Cambridge, Mass.

**National Institutes of Health** (NIH), Bethesda, Md.

**Orphazyme ApS**, Copenhagen, Denmark

**UCB Group** (Euronext:UCB), Brussels, Belgium

**University of Pennsylvania**, Philadelphia, Pa.

**Vtesse Inc.**, Gaithersburg, Md.

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EMERGING COMPANY PROFILE

# ADDING TO IMMUNE FUNCTION

BY EMILY CUKIER-MEISNER, SENIOR WRITER

Admune Therapeutics LLC is developing a heterodimeric complex of IL-15 to boost the immune system's response to cancer immunotherapies by increasing the number of antitumor lymphocytes overall and in the vicinity of tumors.

Tumors' responses to immunotherapy depend in part on the appropriate balance of immune cells that carry out an antitumor response vs. those that promote tolerance. President and CEO Sergio Finkielsztein said higher levels of tumor-infiltrating lymphocytes have been associated with better clinical outcomes, particularly in trials of checkpoint-targeting agents like PD-1 inhibitors.

"That is the whole hypothesis: checkpoint inhibitors and antibody-dependent cellular cytotoxicity are not going to do it on their own. You need to expand the relevant lymphocytes," he said.

Admune plans to begin a Phase I trial of hetIL-15 monotherapy to treat metastatic cancers this month and will seek multiple partners to test combinations, with anti-PD-1 and anti-PD-L1 agents "at the top of the list." The product is a complex of IL-15 with a cleaved soluble form of IL-15 receptor alpha chain (IL-15RA).

The IL-15/IL-15RA complex occurs naturally in both soluble and membrane-bound forms. It forms an activated complex by binding two additional receptor components: the IL-2 receptor beta chain (CD122; IL2RB) and gamma chain (CD132; IL2RG). Activating the receptor complex produces downstream effects that could increase tumor responses to immunotherapy, including proliferation of NK cells, CD8+ and CD4+ cells; migration of T cells to the periphery and tumors; and reduction of the proportion of Treg cells within tumors that could otherwise attenuate antitumor immune responses.

The product resulted from work conducted under a CRADA between Marine Polymer Technologies Inc. and NCI. Marine and NCI were studying ways of combining polymers with cytokines in oncology, which Finkielsztein said led to insights about how to stabilize IL-15. Instability had hampered the molecule's development as a therapeutic.

**ADMUNE THERAPEUTICS LLC**
Danvers, Mass.

**Technology:** Heterodimeric IL-15 complex for immunotherapy

**Disease focus:** Cancer

**Clinical status:** Preclinical

**Founded:** 2013 by Gessam Associates, Pilot House Associates and John Vournakis

**University collaborators:** National Cancer Institute, Cancer Immunotherapy Network, Sunnybrook Research Institute

**Corporate partners:** Undisclosed

**Number of employees:** 10

**Funds raised:** Undisclosed

**Investors:** Gessam Associates, Pilot House Associates

**CEO:** Sergio Finkielsztein

**Patents:** 7 issued covering composition of matter, manufacturing, formulations and therapeutic applications related to heterodimeric IL-15/IL-15RA

"They discovered what was missing was a receptor — half the molecule. When they expressed both IL-15 and the receptor, the resulting molecule was incredibly stable," he said.

In 2013, NCI researchers published mouse data in *The Journal of Biological Chemistry* data showing injection of the IL-15/IL-15RA complex induced proliferation of CD8+ T cell and NK cells more than IL-15 alone.

After Marine and NCI figured out a human cell line production process and subcutaneous delivery, Marine licensed the IP from NCI and spun out Admune to develop hetIL-15.

Finkielsztein said clinical experience with Novartis AG's Proleukin aldesleukin, a recombinant IL-2 to treat metastatic renal cell carcinoma (RCC) and melanoma, has provided proof of concept for expanding lymphocytes to attack tumors.

But IL-15 might be more active because IL-2 interacts with and expands Tregs, which dampen the immune response. IL-15 does not affect Tregs directly, but preferentially expands other lymphocytes that increase antitumor response. And animal studies suggest IL-15 may be less likely to cause capillary leak syndrome, an IL-2-related toxicity for which Proleukin has a black box warning.

"We have a history with IL-2 of expanding lymphocytes. Now we have a way to expand lymphocytes in a safe way," said Finkielsztein.

Admune expects to focus on solid tumors so it can track infiltrating lymphocyte changes during therapy, he said.

Altor Bioscience Corp. also has an IL-15 product in the clinic for cancer. ALT-803 is an IL-15 mutant complexed to an Fc fusion protein of IL-15RA. It is in five Phase I/II trials to treat hematologic and solid tumors.

Finkielsztein said using the biological heterodimer, rather than a fusion protein, might reduce immunogenicity. However, Altor VP of R&D Peter Rhode said ALT-803 is not expected to be highly immunogenic because it contains fewer non-host sequences and is dosed lower than commonly used therapeutic antibodies. He said the product also contains a mutation for increased agonist activity. bc

## COMPANIES AND INSTITUTIONS MENTIONED

**Admune Therapeutics LLC**, Danvers, Mass.
**Altor Bioscience Corp.**, Miramar, Fla.
**Marine Polymer Technologies Inc.**, Burlington, Mass.
**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

# GETTING THE MESSAGE IN MELANOMA

BY EMILY CUKIER-MEISNER, SENIOR WRITER

Initial hand-wringing by FDA reviewers over the statistical robustness and meaningfulness of efficacy data for Amgen Inc.'s talimogene laherparepvec faded away last week when an FDA advisory committee saw a subset of patients they thought received clear benefit, including a suggestion of greatly improved survival.

At the beginning of the meeting, FDA reviewers presented a litany of concerns over the study design and clinical benefit shown in Amgen's lone Phase III trial. The product, T-Vec, met the primary endpoint of durable response rate but narrowly missed the secondary endpoint of overall survival.

The panelists' discussion suggested they have taken to heart the messages delivered by Richard Pazdur in a recent episode of BioCentury TV: looking beyond medians, accepting non-ideal studies if they reveal large efficacy signals and incorporating patient perspectives.

Pazdur, director of the Office of Hematology and Oncology Drug Products at FDA's Center for Drug Evaluation and Research, did not attend Wednesday's joint meeting of FDA's Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee.

Still, as panelists debated the merits of the data, their views coalesced around several exploratory analyses that suggested patients with disease that hadn't metastasized extensively did considerably better on T-Vec than on active control.

"I think we can't ignore that; looking at early stages, those differences are unequivocal," said Antonio Tito Fojo, director of the medical oncology fellowship program at NCI and a permanent voting member of ODAC.

More than one panelist said patient testimony during the meeting's public comment period influenced their "yes" votes.

"The patients who spoke helped me focus. I do not want to take this drug out of the hands of individual oncologists treating melanoma and restrict it to subgroups," said Louis Diehl, a professor of medicine at Duke University and a permanent voting member of ODAC.

Panelists voted 22-1 to recommend approval of T-Vec to treat injectable regionally or distantly metastatic melanoma. The PDUFA date is Oct. 27.

## SUBDIVIDE AND CONQUER

T-Vec is a modified herpes simplex virus type 1 (HSV-1) encoding GM-CSF. It is the first oncolytic virus to undergo FDA review.

It acts by infecting and replicating within tumor cells to destroy them, and by expressing GM-CSF locally to induce an immune response to the antigens released upon tumor death. Amgen obtained T-Vec from its 2011 acquisition of BioVex Inc.

The randomized, open-label Phase III study enrolled 436 patients with unresectable stage IIIb, IIIc or IV melanoma and compared T-Vec to GM-CSF, which was under investigation to treat melanoma when the trial began. T-Vec produced a significantly higher durable response rate vs. GM-CSF (15.6% vs. 1.4%, $p<0.0001$). But the numerical increase on the secondary endpoint of OS just missed statistical significance (23.3 months vs. 18.9 months, $p=0.051$).

Durable response was defined as a complete or partial response lasting for at least 6 months that began within 12 months of starting therapy.

> "THERE ARE TWO PHILOSOPHIES OF DATA ANALYSIS. ONE IS TO NEVER DO SUBSET ANALYSIS AND NEVER BELIEVE SUBSET ANALYSIS, AND THE OTHER IS TO LOOK AT THE DATA AND MAKE THE BEST JUDGMENT YOU CAN."
>
> RICHARD SIMON, NCI

Robert Le, a medical officer in FDA's Office of Cellular, Tissue and Gene Therapies, said the agency didn't think potential bias from the open-label design would change the conclusion that the T-Vec group had more durable responses. But he questioned whether that endpoint reflected meaningful clinical benefit.

"The complicated lesion response and assessment algorithm used to determine which were durable responders raised concerns regarding the reliability of assessment and clinical meaningfulness of disease response, in particular for subjects who experienced progressive disease or developed a new lesion," he said.

Other FDA presenters also questioned the OS trend because early withdrawals from the study were unbalanced between treatment arms, which might have favored T-Vec. They asked panelists to consider T-Vec in the context of recently approved melanoma therapies that have shown OS benefit.

But Amgen's subgroup data suggested the medians weren't telling the whole story, as there was a striking difference in OS benefit between

patients with early vs. later stage disease. In fact, consistent data from subpopulations in the trial helped panelists conclude T-Vec's efficacy was neither a statistical artifact nor clinically meaningless, at least for patients with less severe disease.

For patients with stage III or IVM1a melanoma, median OS was 19.6 months longer for T-Vec than GM-CSF (HR=0.57, CI 0.40-0.80). For stage IVM1b or IVM1c disease, median OS was 2.5 months shorter for the T-Vec group (HR=1.07, CI 0.75-1.52). No p-values were provided.

Stage III melanoma describes disease with at least one affected lymph node and skin lesions confined to a limited region. Stage IVM1a reflects disease at distant skin sites, and IVM1b and IVM1c reflect metastases to lung and other viscera, respectively.

**"I LEAVE IT TO THE CLINICIAN TO DECIDE ABOUT THE OPPORTUNITY COST IN USING THIS TREATMENT VS. ANOTHER TREATMENT, ESPECIALLY FOR THOSE IN LATER STAGES OF THE DISEASE."**

**TABASSUM AHSAN, TULANE UNIVERSITY**

Durable response rate among patients with stage III melanoma receiving T-Vec was 33% vs. 0% for GM-CSF; the difference was less pronounced or reversed for patients with stage IVM1a (16.0% vs. 2.3%), IVM1b (3.1% vs. 3.8%) or IVM1c (7.5% vs. 3.4%).

Richard Simon, chief of the biometric branch of NCI and a temporary voting member, thought the data supported a strong survival benefit for patients without visceral disease, even though they came from exploratory analyses.

"There are two philosophies of data analysis. One is to never do subset analysis and never believe subset analysis, and the other is to look at the data and make the best judgment you can. I believe in the second," he said.

Others were reassured by the response data.

"It looks like when you inject lesions, they shrink. That's a benefit we shouldn't overlook — it can be a very morbid problem for patients," said Patrick Hwu, chair of the Department of Melanoma Medical Oncology at the University of Texas MD Anderson Cancer Center and a temporary voting member.

Panelists' views of T-Vec were bolstered by the therapy's safety profile, which they deemed less toxic than most melanoma treatments. Some expressed concern over cellulitis, safety in immunocompromised patients and risk of transmitting the virus to healthcare providers or persons in close contact with patients, but none said those concerns influenced their vote.

"The actual physical risk to the patient of getting the medicine was very little," said Ann Zovein. She is an assistant professor in the Department of Pediatrics and Cardiovascular Research Institute at the University of California San Francisco, and a permanent voting member of the Cellular, Tissue, and Gene Therapies panel.

However, she said, "I thought there was a modest benefit at best, on dated information," referring to the lack of a comparison to more recently approved therapies.

## NARROW VICTORY

FDA asked the panel to discuss the appropriate population for T-Vec, but did not ask panelists to vote on restricting the indication. Panelists didn't agree on whether or how to restrict T-Vec's use to earlier stages of melanoma studied in the trial.

Richard Sherry, who cast the sole dissenting vote, didn't dispute that some patients could benefit from T-Vec. But he voted against the proposed indication on principle.

"This drug is not appropriate for the vast majority of patients that have visceral disease. When you look at the indications in this trial, there are no limits. And that to me is not clinically acceptable," he said.

Sherry is a staff clinician at the Surgery Branch of NCI and a temporary voting member.

Those who thought T-Vec should be approved for the entire Phase III population didn't necessarily think it would benefit all those patients but preferred to leave the decision to doctors.

"I leave it to the clinician to decide about the opportunity cost in using this treatment vs. another treatment, especially for those in later stages of the disease," said Tabassum Ahsan, an assistant professor in the Department of Biomedical Engineering at Tulane University. Ahsan was acting chair and a temporary voting member at the meeting.

Hwu added, "If someone with multiple brain lesions and lung lesions and liver lesions is going to get this first, before an anti-PD-1, then they need to get another doctor. But I think we don't have the data to micromanage what you should get first or second or third."

## SECOND OPINION

David McDermott, a melanoma and renal cell carcinoma specialist who spoke to BioCentury after the meeting but did not attend it, thought T-Vec showed limited benefit compared to approved melanoma agents, and that its niche would be a narrow one. McDermott is director of the biologic therapy and cutaneous oncology programs at Beth Israel Deaconess Medical Center.

"The typical patient I could see getting this would be someone who has stage III disease who can't be resected, which is relatively uncommon, or IVM1a disease, which happens but is relatively less common than other presentations of metastatic disease," he said.

A dermatologist who treats skin cancers, Priya Nayyar, who also spoke to BioCentury but did not attend the meeting, thought T-Vec wouldn't be the best initial therapy for patients with BRAF mutated melanoma. Nayyar is director of dermatologic surgery at North Shore-LIJ Health System.






"BRAF inhibitors and BRAF-positive melanoma patients have had good response rates. Add the combination of MEK inhibitors, and they do well," she said.

Both McDermott and Nayyar were hopeful that combining T-Vec with other melanoma therapies like anti-PD-1 agents would be more effective, especially for patients with advanced disease.

Amgen is studying T-Vec in combination with Yervoy ipilimumab or Keytruda pembrolizumab to treat patients with unresected melanoma in a pair of Phase I/II trials.

"I think they're smart to move forward with combinations to make what will be the standard treatments better," said McDermott.

Amgen's Kristen Davis said the Yervoy combination trial is scheduled to complete in 2017, and Amgen plans to begin the next phase of the Keytruda combination trial now that the Phase 1b portion is complete.

Yervoy is a human mAb against CTLA-4 (CD152) receptor marketed by Bristol-Myers Squibb Co. Keytruda is a humanized IgG4 mAb against PD-1 marketed by Merck & Co. Inc. Both are approved to treat melanoma. bc

*COMPANIES AND INSTITUTIONS MENTIONED*

**Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.
**Beth Israel Deaconess Medical Center**, Boston, Mass.
**Bristol-Myers Squibb Co.** (NYSE:BMY), New York, N.Y.
**Duke University**, Durham, N.C.
**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.
**National Cancer Institute** (NCI), Bethesda, Md.
**North Shore-LIJ Health System**, New Hyde Park, N.Y.
**Tulane University**, New Orleans, La.
**University of California San Francisco**, San Francisco, Calif.
**University of Texas MD Anderson Cancer Center**, Houston, Texas
**U.S. Food and Drug Administration** (FDA), Silver Spring, Md.

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FINANCE

# GENERAL DEPARTURE

BY STEVE EDELSON, SENIOR EDITOR

Buysiders contacted by BioCentury agree last week's 6% hosing of biotech indices reflects generalist investors exiting the sector. They also expect the companies hardest hit will be early stage biotechs that have seen significant stock rises in recent months.

There's less consensus on whether biotech's convergence with the broader markets is temporary, and how low biotech can go.

Biotechs had been increasingly outpacing the markets since the start of 2012. The acceleration was particularly pronounced from the start of this year to March 19, at which point the BioCentury 100 index was up 26% year to date compared with a 5% gain for the NASDAQ. That gap finally started to shrink last week (see "Convergence").

Craig Johnson, a technical analyst at Piper Jaffray, said biotech indices could fall an additional 10%. He still likes the sector, however, and expects it to remain in an overall uptrend.

Other reasons for optimism include the signs of investors' selective appetite for biotech paper — as evidenced by $549.1 million raised in IPOs and follow-ons last week — and the desire of some buysiders to start buying on the open market stocks they previously deemed too pricey.

## NOT LIKE THE OTHERS

Since the start of the biotech bull run in 2009, there have been five corrections of at least 10%. The biggest decline was also the longest — a 23% slide that stretched from May 31 to Aug. 8, 2011.

The others lasted about five weeks, including the most recent — an 18% decline in the BioCentury 100 from Feb. 27 to April 4, 2014.

It's tempting to say a spring sell-off is becoming an annual tradition, but the circumstances are dramatically different between this year and last.

The steepest part of the 2014 downturn was precipitated by a March 20 letter to Gilead Sciences Inc. from lawmakers that requested pricing information for HCV drug Sovaldi sofosbuvir. That news sent the BioCentury 100 down 12% in a single week.

This time, there was a Phase III blowup for Celladon Corp. in the gene therapy space and an earnings miss for Biogen Inc.; however, there was no single trigger akin to concerns about the sustainability of drug prices.

In addition, this spring's downturn wasn't entirely unexpected. Multiple buysiders told BioCentury in March that the sector was due for a temporary decline that would likely serve to set a new base for continued growth.

## EVACUATION FROM SPECULATION

Whereas Gilead's HCV drug prices accelerated last year's spring downturn, the biotech's boffo 1Q15 earnings postmarket Thursday helped the sector snap out of a four-day tailspin that saw the BioCentury 100 lose 9% of its value. Gilead reported revenues and EPS that eclipsed consensus estimates, thanks to a doubling of its HCV drug sales to $4.6 billion in 1Q15 compared with $2.3 billion in 1Q14. The BioCentury 100 was up 3% on Friday. Gilead jumped 4% to $105.01 on the day.

Even before Gilead's upside surprise, many buysiders were flocking to big caps from both the sidelines and from small cap biotechs. Companies valued at $5 billion or more were up 8.3% in 1Q15, with gainers outnumbering decliners 31-3. The only market cap band that performed better was the $1-$4.9 billion group, which added 9.2%.

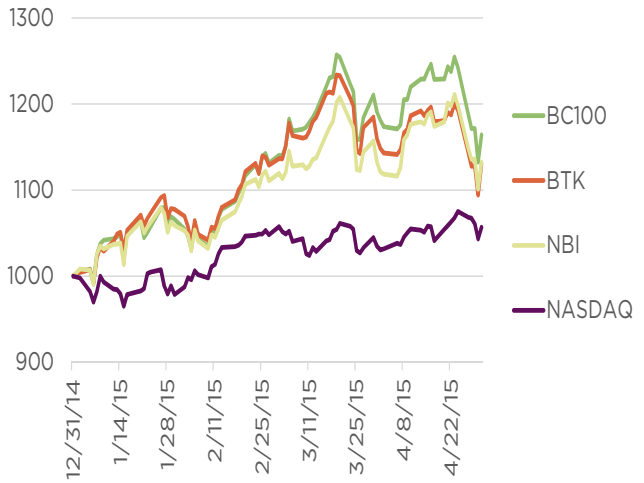
Two days prior to Gilead's earnings, Andy Smith of Mann Bioinvest told BioCentury that the company was "remarkably cheap."

He added: "The big cap stocks are reasonably safe places to be."

Smith said the biotech sector does have some overheated companies. "There are big islands of overvaluation," he said. "Relatively recent IPOs that have tested just a couple of patients in clinical trials and are worth more than $2 billion — that's a big no-no."

### CONVERGENCE

The gap between the BioCentury 100 index and the NASDAQ Composite index reached its widest point on March 19, but has since started to converge. From Dec. 31, 2014, to March 19, 2015, the BC100 gained 26% vs. a 5% gain by the NASDAQ. As of Friday, the BC100 is up 16% year to date, while the NASDAQ is up 6%. Benchmarks indexed to 1,000 as of Dec. 31, 2014.



Thus, he thinks biotech was due for a downturn. "Any sort of increase in life science stocks at the moment is virtually unexplainable unless it's computers trading with one another," he said. "Nevertheless, I can see this as a short-term deflation and not a big correction. Big corrections often don't have anything to do with biotech and instead just see people exiting their high beta holdings."

"I think people are taking their speculative names off the table — that's what I see happening," added Johnson. "I don't see some gigantic rollover in the entire biotech space at this time. It seems like profit taking."

"Some of the generalists are leaving the sector. It's not a time to own speculative, early stage stocks," said Eric Roberts of Valence Fund. "People made money on late-stage companies and then reached for the earlier-stage biotechs. There are a lot of companies that are just science experiments and are getting bid up in valuation. It's really time in the cycle for the air to let out."

## "THE BIG CAP STOCKS ARE REASONABLY SAFE PLACES TO BE."

### ANDY SMITH, MANN BIOINVEST

Some of the hardest hit names have been high-flying, early stage companies in fields such as cancer immunotherapy. For example, Juno Therapeutics Inc. fell $11.84 (21%) to $44.82 last week, and fellow CAR T company Kite Pharma Inc. shed $9.17 (15%) to $51.41.

Those losses were on top of double-digit percent declines the prior week as investors grappled with some of the first solid tumor data for a CAR T program that came from Novartis AG and the University of Pennsylvania.

Prior to the solid tumor data, Juno was up 24% on the year, and Kite was up 13%.

"Some of the selling is specific to therapeutic areas," noted Marshall Gordon of ClearBridge Investments. "Either people are perceiving more technical risk, or the valuations were stretched to begin with. I'm hard-pressed to say it's surprising. I happen to believe that for some companies to have achieved the valuations they have, there's more than just sector specialists that got into the stocks. The non-specialists may not be able to appreciate the nuance between different programs, so when you have news like Celladon people are throwing the baby out with the bathwater."

Celladon's Phase IIb data for its Mydicar gene therapy to treat heart failure was an eagerly anticipated 2Q15 milestone. The stock shed 81% last Monday after the trial failed.

Other gene therapy stocks were mixed. Hardest hit was Avalanche Biotechnologies Inc., which fell 12% last week. Spark Therapeutics Inc. and uniQure N.V. fared better but still lost 5% and 6%, respectively. bluebird bio Inc. ended the week up 2%.

Spark was one of the best performing biotechs in 1Q15, when the company saw its share price surge by 237%.

### SHORT-TERM PAIN, LONG-TERM GAIN

None of the buysiders were mourning the smaller number of generalists in the sector.

Typical was Oleg Nodelman of EcoR1 Capital, who said, "Any move that shakes out weak holders strengthens the sector for those of us who are fundamentally driven and long term-oriented."

"I think it's healthy that biotechs have come down," added Alex Denner of Sarissa Capital Management. "There are individual names that are good, but the sector overall is at the high end of valuation. We spent all of last year highly underinvested because we didn't have enough ideas that were cheap enough."

Some specialists may use the downturn to put some of their cash to work.

"I still remain constructive on the longer-term outlook and have a number of companies that I like fundamentally but haven't invested in due to price," added AXA Framlington's Linden Thomson.

She said she'll revisit those names "if a better entry point arises," and cautioned that the downturn could be more prolonged than the five-week slide last spring.

"I do think the current turbulence we are going through is likely to scare more generalists away than usual given how amazingly fast it has been, but hopefully fundamentals will eventually drive things back in the end," said Brad Loncar of Loncar Investments. "I'm now starting to see some biotech stocks that I think are buyable, so it makes me think this is just a healthy pullback and not a bubble so to speak. Hopefully it's a sign of light at the end of the tunnel, too, so maybe we can at least form a base here pretty soon." bc

*COMPANIES AND INSTITUTIONS MENTIONED*

**Avalanche Biotechnologies Inc.** (NASDAQ:AAVL), Menlo Park, Calif.
**Biogen Inc.** (NASDAQ:BIIB), Cambridge, Mass.
**bluebird bio Inc.** (NASDAQ:BLUE), Cambridge, Mass.
**Celladon Corp.** (NASDAQ:CLDN), San Diego, Calif.
**Gilead Sciences Inc.** (NASDAQ:GILD), Foster City, Calif.
**Juno Therapeutics Inc.** (NASDAQ:JUNO), Seattle, Wash.
**Kite Pharma Inc.** (NASDAQ:KITE), Los Angeles, Calif.
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland
**Spark Therapeutics Inc.** (NASDAQ:ONCE), Philadelphia, Pa.
**uniQure N.V.** (NASDAQ:QURE), Amsterdam, the Netherlands
**University of Pennsylvania**, Philadelphia, Pa.

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**Edelson, S.** "CAR talk." *BioCentury* (2015)
**Edelson, S.** "It's the milestone, CUPID." *BioCentury* (2015)
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**Hansen, S.** "Fundamental rally." *BioCentury* (2015)

EBB & FLOW

# BUILD TO BYE-BYE

Versant Ventures last week saw its first build-to-buy company get taken out by Celgene Corp. (NASDAQ:CELG) and another enter into a partnership with Celgene, but the VC doesn't expect its recently closed fifth fund to dramatically ramp up such deals vs. its prior fund.

The reason, said Versant's Brad Bolzon, is "de novo deals of this sort take significant time and resources. We need to be selective about the programs we wish to construct around the model and about choosing the partners wisely."

The firm kicked off last week with news that Celgene is buying portfolio company Quanticel Pharmaceuticals Inc. for $100 million up front and up to $385 million in R&D and regulatory milestones. The Celgene deal was about three and a half years in the making — Celgene received an option to acquire Quanticel in November 2011, at which time it committed $45 million to the newco (see BioCentury, Nov. 14, 2011).

Quanticel's platform performs single-cell genomic analysis of tumors. The company also has a basket of preclinical oncology candidates that target undisclosed epigenetic modifiers. Multiple candidates are due to enter clinical testing in early 2016.

Versant was the sole venture investor in Quanticel and invested $10 million in the company starting in 2011. The Quanticel ownership stakes of management and Celgene are undisclosed. Still, the $100 million up front price is 10x what Versant invested.

On Wednesday, Celgene partnered with another Versant company, Northern Biologics Inc., to develop a portfolio of preclinical antibodies to treat cancer and fibrosis. Northern will receive $30 million up front and is eligible for undisclosed additional payments. Celgene has an option to in-license products from the collaboration and has the right to buy Northern Biologics when the deal completes in three to four years, depending on achievement of undisclosed milestones.

Northern Biologics is the first company that emerged from Versant's Toronto-based Blueline Bioscience incubator.

Bolzon said a key feature of both build-to-buy deals is "a portfolio of drug candidates, plus a platform based on first-in-class discoveries from academia, plus a team."

Versant has five build-to-buy companies in its fourth fund. Bolzon said the number is likely to be similar in the fifth fund, which closed at $305 million in December 2014 (see BioCentury, Dec. 15, 2014).

The fifth fund already has two build-to-buy companies, one of which is Northern Biologics.

*—Steve Edelson*

**"WE NEED TO BE SELECTIVE ABOUT THE PROGRAMS WE WISH TO CONSTRUCT AROUND THE MODEL."**

**BRAD BOLZON, VERSANT**

## VALUING INTARCIA

Intarcia Therapeutics Inc.'s new royalty investors are betting the biotech can more than triple its current $1.75 billion valuation in the next four years. The company already has done it once, roughly tripling its value from $635 million in 2012.

Last week, Intarcia received $225 million from undisclosed investors in exchange for a 1.5% royalty on future global sales of ITCA 650, which is in Phase III testing to treat Type II diabetes. The once-yearly product provides continuous subcutaneous delivery of the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide via the implantable Duros osmotic minipump. Intarcia expects to submit an NDA to FDA in 1H16 and hopes to launch ITCA 650 in 2017.

**"THIS ESSENTIALLY FINANCES THE COMPANY AT A $5.5 BILLION VALUATION."**

**KURT GRAVES, INTARCIA**

Royalty investors typically aren't interested in a company's stock price and valuation, but this deal is different. The reason is the syndicate has an option to hand back its royalty rights in exchange for Intarcia common stock that corresponds to a company valuation of $5.5 billion. The clock on the option starts ticking upon FDA approval of ITCA 650 and expires either two years later or on Dec. 31, 2019, whichever comes later.

Intarcia plans to use the proceeds from the financing to run head-to-head comparison and switch studies of ITCA 650 vs. approved oral and injectable diabetes drugs, and to build infrastructure to launch ITCA 650 in the U.S. The company also will use the money to advance its recently acquired pipeline. In March, Intarcia partnered with Numab AG to develop once- or twice-yearly monospecific and multispecific antibodies to treat diabetes, obesity and autoimmune diseases.

"The royalty deal gives investors a financial return on the lead asset, but if you convert to stock you get the upside of the pipeline as well," said Chairman, President and CEO Kurt Graves. "This essentially finances the company at a $5.5 billion valuation."

Graves said that if the investors convert their royalty interest into stock, they would own a low single-digit percentage of Intarcia. "Everyone tells me we could have gone public a long time ago. But then you have to ask yourself, what amount of dilution would we take going public vs. the deal we just did? It was a no-brainer for us."

In the past five years, Intarcia has raised more than $1 billion in venture rounds and non-dilutive financings.

*—Steve Edelson*

## SWORDS TO PLOWSHARES

Sarissa Capital Management succeeded in prompting the retirement of Harvey Berger from Ariad Pharmaceuticals Inc. (NASDAQ:ARIA), but the outgoing chairman and CEO has a vested interest in the activist investor's ability to unlock value in the cancer company.

According to SEC filings, Berger directly held 1.3 million Ariad shares as of March 26 and indirectly held another 2.4 million shares as of Feb. 12, which translates to a total stake of about 2%.

Sarissa began pushing for Berger's retirement in February with a proxy battle, and Wednesday's settlement — which pushed the stock up $0.36 to $9.23 — increased the value of Berger's total holdings by 4% to $34 million from $32.6 million. Ariad ended the week at $9.15.

Berger told BioCentury those figures don't include options. He estimated that his total ownership, taking options into account, is in the ballpark of 5%.

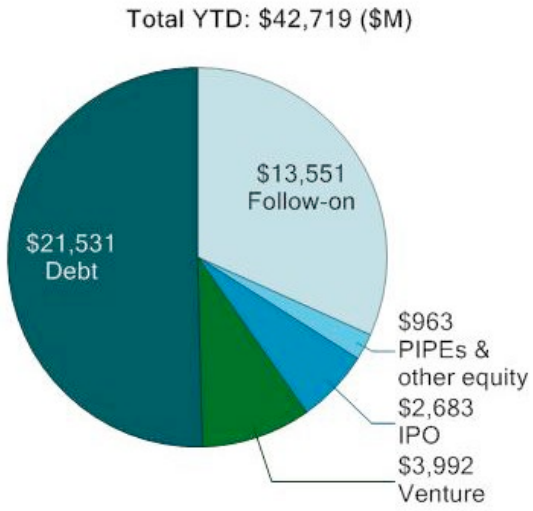
"The options vest on a certain date after I retire, and then remain exercisable on their original terms," he added.

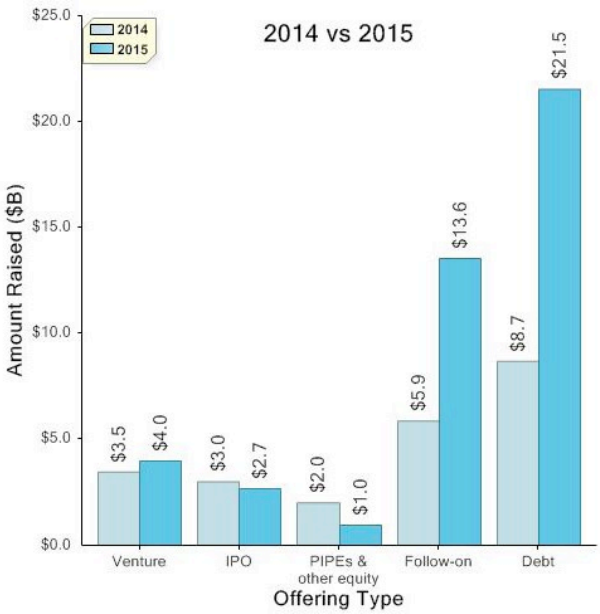
Berger will retire when the search committee of Ariad's board names a successor or on Dec. 31, 2015, whichever comes earlier. Sarissa's Alex Denner will chair the committee.

"We'll move expeditiously to find a strong CEO to revitalize the company," Denner told BioCentury.

## MONEY RAISED IN 2015

Last week, the biotech industry raised $1,021 million, bringing to $42.7 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 overallotments and warrants, and are rounded to the nearest millions.



Sarissa withdrew the three nominees it had hoped to install, but it did get one of the trio on the board in the settlement — Mersana Therapeutics Inc. President and CEO Anna Protopapas.

"I expect to be at Ariad most of this year, and my complete focus from now until I leave is to drive the company forward to milestones," Berger said. Those milestones include starting trials of Iclusig ponatinib in earlier lines of leukemia than the drug's marketed indication, and securing a partnership for brigatinib (AP26113), a dual inhibitor of ALK and EGFR that is in a pivotal Phase II trial to treat ALK-positive non-small cell lung cancer (NSCLC).

Sarissa began buying Ariad after FDA placed Iclusig on partial clinical hold based on data showing longer use was associated with increased risk of thrombotic events. The firm built a 6.2% position over Oct. 9-22, 2013, when Ariad traded between $2.62 and $6.10.

At the end of that month, FDA temporarily suspended marketing of the pan-BCR-ABL tyrosine kinase inhibitor. Iclusig reentered the market in January 2014. A month later Denner joined Ariad's board.

Sarissa owned 6.9% of Ariad as of Tuesday. bc

*—Steve Edelson*

## CORRECTION

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

Cytokinetics Inc. (NASDAQ:CYTK), South San Francisco, Calif.

Business: Cardiovascular

Amgen has exclusive worldwide rights to omecamtiv mecarbil from Cytokinetics. The April 27 edition of *BioCentury* misstated the territories.

## Analyst picks & changes

| Company | Bank | Analyst | Coverage | Opinion | Wk chg | 5/1 cls |
|---|---|---|---|---|---|---|
| **Agios Pharmaceuticals Inc.** (NASDAQ:AGIO) | Canaccord | John Newman | Downgrade | Hold (from buy) | -11% | $95.74 |
| Newman also lowered his target to $103 from $163 after Agios announced plans last week to begin clinical testing of AG-881 for glioma in 2Q15, which Newman believes suggests higher risk regarding the company's more advanced AG-120. He suspects Agios is moving AG-881 forward because the ongoing open-label Phase I trial of AG-120 in solid tumors, including glioma, is not showing encouraging data. The company expects to report data from the AG-120 trial in 2H15, which is later than Newman had expected. AG-881 is an inhibitor of mutated isocitrate dehydrogenase 1 (IDH1) and IDH2 and AG-120 is an inhibitor of IDH1. **Celgene Corp.** (NASDAQ:CELG) has exclusive, ex-U.S. rights to AG-120, and the partners are co-developing AG-881. | | | | | | |
| **Celladon Corp.** (NASDAQ:CLDN) | H.C. Wainwright | Ching-Yi Lin | Downgrade | Neutral (from buy) | -81% | $2.62 |
| | Roth Capital Partners | Elemer Piros | Downgrade | Neutral (from buy) | | |
| | Wedbush | David Nierengarten | Downgrade | Neutral (from buy) | | |
| Lin downgraded and removed her $31 target after Mydicar missed the primary and secondary endpoints in the Phase IIb CUPID 2 trial to treat heart failure. Lin said the miss was substantial enough that she does not see a path forward to approval. Mydicar is a recombinant adeno-associated viral (AAV) vector bearing the gene for ATPase Ca++ transporting cardiac muscle slow twitch 2 (ATP2A2; SERCA2A), which is found in the sarcoplasmic reticulum. | | | | | | |
| Piros also lowered his target to $2 from $70 on the Mydicar miss and believes the company will likely discontinue development of the product for heart failure and other indications as well. | | | | | | |
| Nierengarten also lowered his target to $3 from $29 on the Mydicar miss. | | | | | | |
| **Pacific Biosciences of California Inc.** (NASDAQ:PACB) | William Blair | Amanda Murphy | Upgrade | Outperform (from market perform) | -2% | $5.67 |
| Murphy upgraded, saying the 34% year-to-date pullback in Pacific Biosciences' stock represents a buying opportunity. She believes the sequencing company has made "significant and impressive progress" over the past few years in its chemistry, improving both throughput and read length of its sequencing systems. Murphy added that her recent survey suggests that the company's platforms "are being well utilized, suggesting potential for consumable upside throughout the year." Murphy estimates 2015 revenues of $72.5M. | | | | | | |

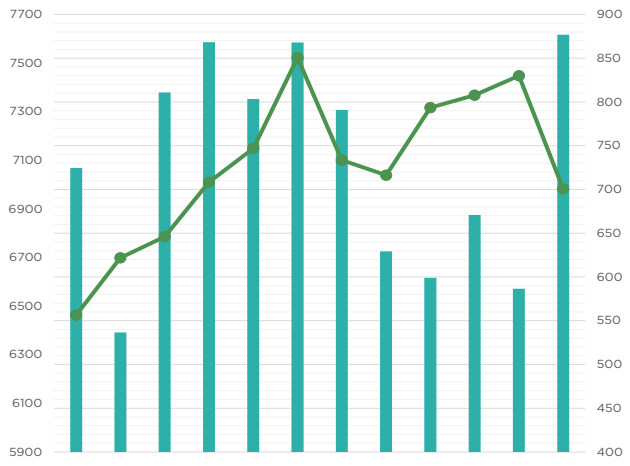
# EARNINGS ON DECK

At least 18 biotechs are expected to report earnings this week. (A) Fiscal 3Q; (B) Fiscal 2Q; (C) Being acquired by **Merck KGaA** (Xetra:MRK); (D) Fiscal 2014.

| Company | Date | Pre/post mkt | 1Q15 EPS est | 1Q14 EPS | Expected chg |
|---|---|---|---|---|---|
| **Luminex Corp.** (NASDAQ:LMNX) | 5/4 | Post | $0.12 | $0.14 | -14% |
| **Bio-Techne** (NASDAQ:TECH) (A) | 5/5 | Pre | $0.90 | $0.94 | -4% |
| **The Medicines Co.** (NASDAQ:MDCO) | 5/5 | Pre | -$0.88 | -$0.08 | NA |
| **Bio-Rad Laboratories Inc.** (NYSE:BIO) | 5/5 | Post | $0.33 | $0.57 | -42% |
| **Myriad Genetics Inc.** (NASDAQ:MYGN) (A) | 5/5 | Post | $0.39 | $0.48 | -19% |
| **Vivus Inc.** (NASDAQ:VVUS) | 5/5 | Post | -$0.22 | -$0.15 | NA |
| **MorphoSys AG** (Xetra:MOR; Pink:MPSYF) | 5/5 | NA | NA | €0.04 | NA |
| **Qiagen N.V.** (Xetra:QIA; NASDAQ:QGEN) | 5/5 | NA | $0.22 | $0.22 | 0% |
| **Bruker Corp.** (NASDAQ:BRKR) | 5/6 | Post | $0.10 | $0.11 | -9% |
| **GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK) | 5/6 | NA | 17.36p | 21p | -17% |
| **H. Lundbeck A/S** (CSE:LUN) | 5/6 | NA | DKK0.07 | DKK1.69 | -96% |
| **Becton Dickinson and Co.** (NYSE:BDX) (B) | 5/7 | Pre | $1.53 | $1.53 | 0% |
| **Regeneron Pharmaceuticals Inc.** (NASDAQ:REGN) | 5/7 | Pre | $2.71 | $2.26 | 20% |
| **Emergent BioSolutions Inc.** (NYSE:EBS) | 5/7 | Post | -$0.44 | -$0.40 | NA |
| **Jazz Pharmaceuticals plc** (NASDAQ:JAZZ) | 5/7 | Post | $2.14 | $1.61 | 33% |
| **Spectrum Pharmaceuticals Inc.** (NASDAQ:SPPI) | 5/7 | Post | -$0.09 | -$0.44 | NA |
| **Sigma-Aldrich Corp.** (NASDAQ:SIAL) (C) | 5/7 | NA | $1.08 | $1.06 | 2% |
| **Mitsubishi Tanabe Pharma Corp.** (Tokyo:4508) | 5/8 | NA | NA | ¥80.92 (D) | NA |

## BIOCENTURY 100 PRICE & VOLUME TREND

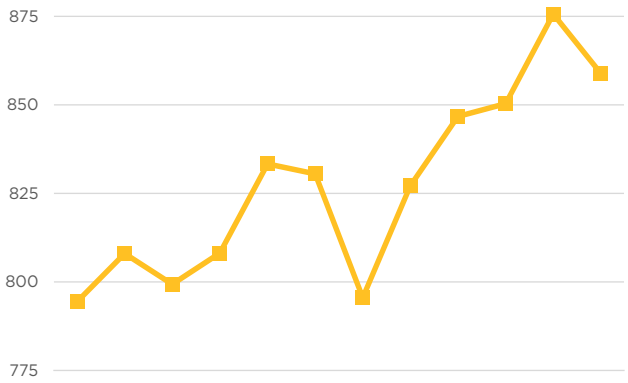
Cumulative weekly performance of 100 bioscience stocks. 12-week period. Line shows Price Level change (Left scale. Index base=1000 on May 10, 1996). Bars show cumulative volume in millions (right scale).




BioCentury tracks 774 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 5/1/15

**PRICES**
6982.75
dn 6%

**VOLUME**
876.9M shrs
up 49%

## PRICE GAINS

Stocks with greatest % price increase in the week ended 5/1. (Priced above $2; 5,000 minimum share volume)

| Company | Ticker | $Close | $Chg | % Chg | Vol(00) |
|---|---|---|---|---|---|
| Kolon Life Science | 102940 | W88500 | W16000.00 | 22% | 12982 |
| Wilex | WL6 | €4.330 | €0.742 | 21% | 4095 |
| Swedish Orphan Biovitrum | SOBI | SEK134.00 | SEK22.300 | 20% | 119786 |
| Can-Fite[1] | CANF | 2.600 | 0.430 | 20% | 283096 |
| Eleven Biotherapeutics | EBIO | 13.310 | 2.120 | 19% | 9446 |
| Saniona | SANION | SEK22.000 | SEK3.500 | 19% | 8233 |
| PeptiDream | 4587 | ¥11440.00 | ¥1740.000 | 18% | 16170 |
| Galapagos[2] | GLPG | €37.570 | €5.570 | 17% | 25520 |
| Innate Pharma | IPH | €15.650 | €2.300 | 17% | 163398 |

## PRICE DECLINES

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

| Company | Ticker | $Close | $Chg | % Chg | Vol(00) |
|---|---|---|---|---|---|
| Celladon | CLDN | 2.620 | -11.060 | -81% | 469295 |
| Atara Biotherapeutics | ATRA | 40.450 | -19.440 | -32% | 14042 |
| Affimed | AFMD | 8.260 | -3.460 | -30% | 13635 |
| Asterias | AST | 10.540 | -4.230 | -29% | 11430 |
| CytRx | CYTR | 3.700 | -1.430 | -28% | 86801 |
| Aduro Biotech | ADRO | 26.090 | -9.910 | -28% | 38951 |
| Carbylan Therapeutics | CBYL | 5.420 | -2.030 | -27% | 5808 |
| Aerie Pharmaceuticals | AERI | 9.370 | -3.500 | -27% | 167081 |
| Advaxis | ADXS | 17.070 | -6.270 | -27% | 122144 |
| Calithera Biosciences | CALA | 9.820 | -3.590 | -27% | 18171 |

## VOLUME GAINS

Greatest changes in volume above 5,000 shares.

| Company | Ticker | Vol(00) | %Chg | $Close | $Chg |
|---|---|---|---|---|---|
| Circassia | CIR | 35991 | 2160% | 300p | 6p |
| Can-Fite[1] | CANF | 283096 | 1735% | 2.600 | 0.430 |
| Poxel | POXEL | 11093 | 1615% | €11.700 | €1.220 |
| PeptiDream | 4587 | 16170 | 1201% | ¥11440.000 | ¥1740.000 |
| Paratek | PRTK | 13264 | 1074% | 25.510 | -3.360 |
| CB Pharma | CNLM | 116 | 1060% | 9.880 | 0.060 |
| Celladon | CLDN | 469295 | 450% | 2.620 | -11.060 |
| Wilex | WL6 | 4095 | 415% | €4.330 | €0.742 |
| Human Metabolome | 6090 | 1436 | 397% | ¥1095.000 | -¥73.000 |
| Ascendis[3] | ASND | 10986 | 384% | 17.550 | -2.450 |

1. Includes volume from Tel Aviv Stock Exchange and converted ADSs (1ADS = 2 shares).
2. Includes volume from Euronext and The Pink Sheets.
3. Volume reflects ADS (1ADS = 1 share).

## BIOCENTURY 100 ADVANCE-DECLINE TRENDS

| Week ended | BC100 Price Level | BC100 Stocks gaining | Gaining vol. (00) | BC100 Stocks declining | Declining vol. (00) |
|---|---|---|---|---|---|
| Apr 03 | 7039.49 | 42 | 2517957 | 58 | 3741051 |
| Apr 10 | 7317.07 | 88 | 5411747 | 12 | 577216 |
| Apr 17 | 7368.70 | 44 | 3469192 | 54 | 2979763 |
| Apr 24 | 7448.49 | 57 | 3853876 | 43 | 2011973 |
| May 01 | 6982.75 | 13 | 1857131 | 87 | 6911945 |

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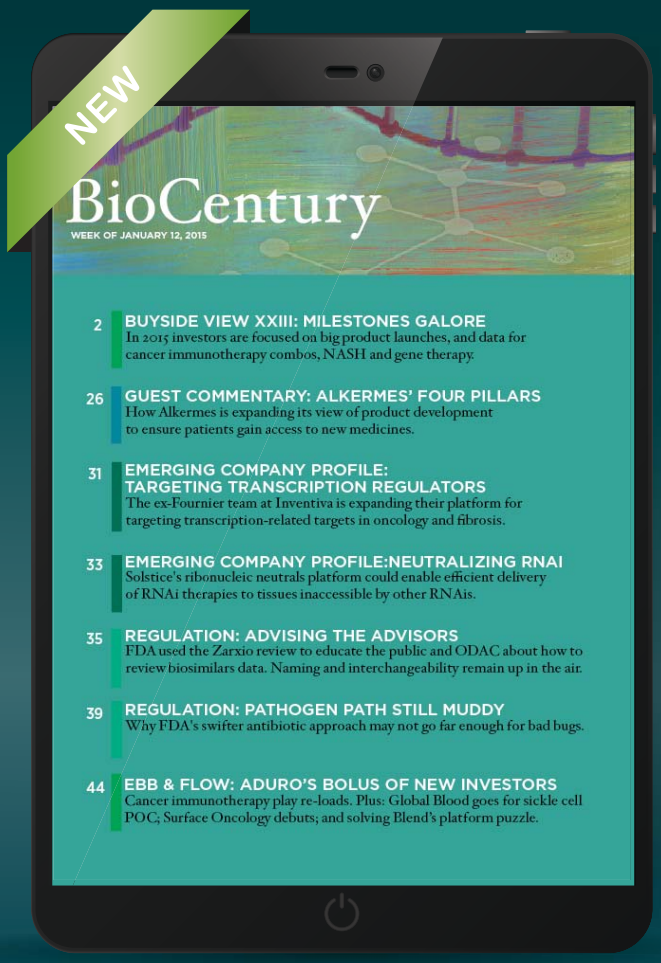


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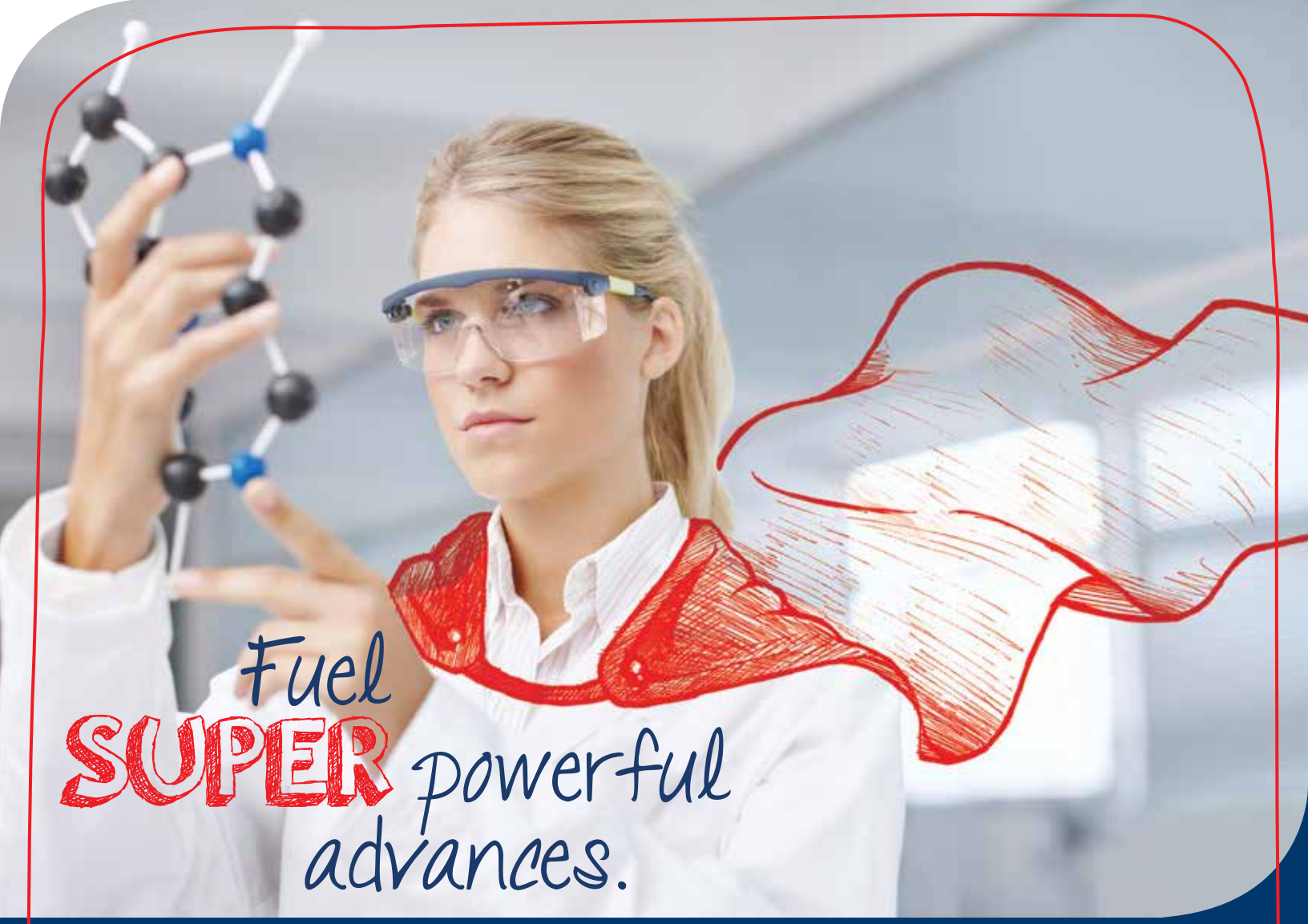


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WEEK IN REVIEW | POWERED BY BCIQ

WEEK OF MAY 4, 2015



COMPANY NEWS

## DEALS

**Aethlon Medical Inc.** (OTCQB:AEMD), San Diego, Calif.
**Thomas Jefferson University**, Philadelphia, Pa.

Business: Pharmacogenetics

Aethlon's Exosome Sciences Inc. subsidiary partnered with the university to evaluate a liquid biopsy platform. The partners will seek to determine whether exosome-based molecular signatures in blood samples from head and neck cancer patients with oral cavity tumors correlate with and predict patient responses to treatment. The investigators will initially focus on exosome-associated RNA. The university declined to disclose financial terms, and Aethlon could not be reached.

**Affymetrix Inc.** (NASDAQ:AFFX), Santa Clara, Calif.
**MTI Ltd.** (Tokyo:9438), Tokyo, Japan

Business: Genomics

Affymetrix and MTI's EverGene Ltd. subsidiary partnered for genetic research and personal genomics services in Japan. Affymetrix is supplying to EverGene custom genotyping arrays based on its Axiom Genotyping Solution for the companies' research program and for use on EverGene's DearGene Starter Kit, which evaluates disease-onset risk. Takara Bio Inc. (Tokyo:4974, Shiga, Japan) will process the samples. Affymetrix declined to disclose financial details, and MTI could not be reached.

**Agios Pharmaceuticals Inc.** (NASDAQ:AGIO), Cambridge, Mass.
**Celgene Corp.** (NASDAQ:CELG), Summit, N.J.

Business: Cancer

Agios granted Celgene worldwide rights to develop and commercialize AG-881, an inhibitor of mutated isocitrate dehydrogenase 1 (IDH1) and IDH2. Agios said it expects a Phase I trial of AG-881 to begin this quarter. The company declined to discuss the indication it will pursue but said preclinical studies of the compound have shown potential in treating glioma. Agios will receive $10 million up front and is eligible for up to $70 million in regulatory milestones. The companies will equally share development costs and global profits. Celgene will book sales and lead ex-U.S. commercialization. Agios will lead U.S. commercialization.

**Bind Therapeutics Inc.** (NASDAQ:BIND), Cambridge, Mass.
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.

Business: Cancer

Bind and Pfizer added two undisclosed Pfizer cancer compounds and extended to March 2016 a 2013 deal under which the companies partnered to develop and commercialize Accurins using undisclosed small molecules provided by the pharma for undisclosed diseases. The target date for Pfizer's exclusive option to license the Accurins remains September. Bind said the companies mutually agreed to extend the research term to ensure the project is ready for pre-IND trials (see BioCentury, April 8, 2013).

**Boehringer Ingelheim GmbH**, Ingelheim, Germany
**Hydra Biosciences Inc.**, Cambridge, Mass.

Business: Renal

Boehringer partnered with Hydra to identify small molecule inhibitors of transient receptor potential (TRP) ion channels, with a primary focus on treating renal diseases. Boehringer is responsible for global development and commercialization of compounds identified under the deal. Hydra is eligible for undisclosed upfront and milestone payments, R&D funding and tiered royalties. The companies declined to provide further details.

**Cellaria Biosciences LLC**, Boston, Mass.
**Taconic Biosciences Inc.**, Hudson, N.Y.
Business: Supply/Service

The companies partnered to improve patient-derived xenografts in animal models for oncology and immuno-oncology research. The partners will create breast cancer cell lines from Taconic's patient-derived xenografts licensed from the University of Utah (Salt Lake City, Utah). Taconic could not provide additional details, and Cellaria could not be reached.

**Cincinnati Children's Hospital Medical Center**, Cincinnati, Ohio
**Shire plc** (LSE:SHP;NASDAQ:SHPG), Dublin, Ireland
Business: Pharmaceuticals

Shire and the medical center partnered under a three-year deal to discover and develop therapies to treat rare diseases, including gastroenterology, nephrology and neurology indications. The center will receive an upfront payment from Shire, which has the right to fund and offer scientific support to selected research programs. The partners aim to produce a development candidate in less than three years. Shire has an exclusive option to license further development and commercialization rights to programs discovered under the deal.

**Curiox Biosystems Pte. Ltd.**, Singapore
**Agency for Science, Technology and Research**, Singapore
Business: Diagnostic

Curiox partnered with the Agency for Science, Technology and Research (A*STAR) over an 18-month term to validate Curiox's DropArray system to make immunomonitoring more cost-efficient. Curiox will provide consumables, technical support and expertise for the assay development. A*STAR's Singapore Immunology Network (SIgN) research institute will evaluate DropArray's compatibility with multiplex assay technology from Luminex Corp. (NASDAQ:LMNX, Austin, Texas). A*STAR's Institute of Molecular and Cellular Biology will also optimize the DropArray system for RNA transfection with suspension cells. A*STAR said the DropArray system can reduce overall assay costs by about 65%. A*STAR declined to disclose financial terms, and Curiox did not respond to inquiries.

**Cytos Biotechnology AG** (SIX:CYTN), Schlieren, Switzerland
**Novartis AG** (NYSE:NVS;SIX:NOVN), Basel, Switzerland
Business: Neurology

Novartis will pay Cytos CHF4 million ($4.2 million) to eliminate payment obligations for CAD106, an Alzheimer's disease (AD) vaccine the companies discovered under a 2001 deal. Novartis is developing the vaccine containing beta amyloid 1-6 peptide coupled to the virus-like particle Qb, which has completed multiple Phase II trials. An NDA submission is slated for after 2019. Cytos could not provide details in time for publication, and Novartis did not disclose financial terms (see BioCentury, Oct 29, 2001).

**4D Molecular Therapeutics LLC**, San Francisco, Calif.
**Roche** (SIX:ROG;OTCQX:RHHBY), Basel, Switzerland
Business: Pharmaceuticals

Roche and 4D partnered to develop and commercialize adeno-associated viral (AAV) vectors identified using 4D's Directed Vector Evolution vector discovery platform. 4D will generate the vectors and optimize them for specific tissue types and transgene payloads. Roche will have exclusive, worldwide rights to develop and commercialize vectors against undisclosed diseases. 4D received an undisclosed upfront payment and is eligible for undisclosed milestones, R&D funding and royalties. The companies declined to disclose financial terms.

**Hebrew University of Jerusalem**, Jerusalem, Israel
**Hadassah Medical Organization**, Jerusalem, Israel
**The Kennedy Trust for Rheumatology Research**, London, U.K.
**ISA Scientific Inc.**, Salt Lake City, Utah
Business: Cardiovascular, Endocrine/Metabolic, Inflammation

The university's Yissum Research Development Co. Ltd. technology transfer company, Hadassah Medical Organization's Hadasit Ltd. technology transfer company and the Kennedy Trust granted ISA exclusive, worldwide rights to patents covering the use of cannabidiol to treat diseases that include diabetes, inflammatory diseases and cardiovascular disorders. The non-psychoactive naturally derived small molecule only found in *Cannabis* is in Phase I trials, with data expected by October. Yissum, Hadassah and The Kennedy Trust could not provide details in time for publication.

**Ichor Medical Systems Inc.**, San Diego, Calif.
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.
Business: Infectious, Drug delivery

Ichor and Johnson & Johnson's Janssen Pharmaceuticals Inc. subsidiary will combine Janssen's preclinical DNA-based HBV vaccine candidates and Ichor's TriGrid electroporation technology for clinical administration. Ichor is eligible for up to $85 million in upfront, R&D and milestone payments, plus royalties. Janssen will be responsible for undisclosed development costs and all

commercialization costs, including manufacturing and distribution for TriGrid. The companies declined to provide further financial terms.

**Institut Curie**, Paris, France
**Theravectys S.A.**, Paris, France
Business: Cancer

The institute granted Theravectys exclusive, worldwide rights to a library of synthetic humanized camelid nanobodies. The company said the deal strengthens its immunotherapeutic platform. Specifically, Theravectys acquired rights to the library to generate receptors for chimeric antigen receptor (CAR)- and T cell receptor (TCR)-based therapies; to identify checkpoint inhibitors; and to screen tumor antigens. Additionally, Theravectys and Institut Curie partnered to optimize the library and develop undisclosed Theravectys' immuno-oncology programs. The partners expect to be able to identify nanobodies from the library in less than six months. The companies could not provide additional details in time for publication.

**Medicines for Malaria Venture**, Geneva, Switzerland
**Merck Serono S.A.**, Geneva, Switzerland
Business: Infectious

Medicines for Malaria Venture granted Merck Serono exclusive rights to develop and commercialize DDD107498, a preclinical antimalarial compound. The partners did not disclose financial terms.

**Merck KGaA** (Xetra:MRK), Darmstadt, Germany
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.
Business: Cancer

The companies finalized their agreement to co-promote Pfizer's Xalkori crizotinib. The companies will co-promote the advanced non-small cell lung cancer (NSCLC) drug in the U.S., Canada, Japan, France, Germany, Italy, Spain and the U.K. starting in 2Q15 and 3Q15. Merck's Merck Serono unit will co-promote the product in the U.S. and Canada. Starting in 2016, the companies will co-promote the product in China and Turkey.

This year, Merck will receive an undisclosed reimbursement for its promotion of Xalkori. Starting next year, Pfizer and Merck will share profits 80/20. The co-promotion term will last through Dec. 31, 2020, in the U.S., Canada, Japan, France, Germany, Italy, Spain and the U.K. and from Jan. 1, 2016, through Dec. 31, 2021, in China and Turkey. Pfizer will report sales in countries where it is co-promoted with Merck. The companies announced the co-promotion as part of a larger co-development and co-commercialization deal last year. Pfizer declined to provide further financial terms, and Merck could not be reached (see BioCentury, Nov. 24, 2014).

**Mylan N.V.** (NASDAQ:MYL), Canonsburg, Pa.
**Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA), Petah Tikva, Israel
Business: Generics

Mylan's board unanimously rejected an unsolicited bid from Teva to acquire the company for $82 per share, or about $40.1 billion. Mylan said the offer "grossly undervalues" the company, reiterated concerns that the combination may violate anti-trust regulations and stood by its offer to acquire Perrigo Co. plc (NYSE:PRGO; Tel Aviv:PRGO, Dublin, Ireland), which Perrigo has rejected three times (see BioCentury, April 27).

After the rejection, Teva sent a letter to Mylan's board reiterating its commitment to the offer, which is contingent on Mylan not acquiring Perrigo. Teva believes it would be able to complete the transaction by year-end.

**Northern Biologics Inc.**, Toronto, Ontario
**Celgene Corp.** (NASDAQ:CELG), Summit, N.J.
Business: Autoimmune, Cancer

Celgene gained the exclusive option to license drug candidates from Northern Biologics and to acquire Northern at the end of the deal, which will be triggered by an undisclosed clinical milestone. Northern Biologics is developing therapeutic antibodies against undisclosed targets in oncology and fibrosis. Northern Biologics said some preclinical candidates may enter clinical testing in two to three years. Celgene paid $30 million up front and will fund the majority of the development costs. The companies declined to provide details.

**PeptiDream Inc.** (Tokyo:4587), Tokyo, Japan
**Novartis AG** (NYSE:NVS;SIX:NOVN), Basel, Switzerland
Business: Pharmaceuticals

Novartis exercised its option under a 2012 deal for non-exclusive rights to PeptiDream's Peptide Discovery Platform System (PDPS) technology. PeptiDream will receive multistage upfront payments and is eligible for undisclosed development milestones and royalties. The companies declined to disclose further financial terms. PDPS enables incorporation of modified unnatural amino acids into mRNA display peptide libraries (see BioCentury, Oct. 1, 2012 & Nov. 19, 2012).

**Perrigo Co. plc** (NYSE:PRGO;Tel Aviv:PRGO), Dublin, Ireland
**Mylan N.V.** (NASDAQ:MYL), Canonsburg, Pa.
Business: Autoimmune, Generics

Perrigo rejected another offer by Mylan to acquire Perrigo. The increased offer, made on April 29, valued the company at $212.01 per share, or $31 billion based on 146.3 million shares on April 24. Specifically, the new offer valued each Perrigo share at $75 in cash plus 2.3 Mylan shares, valued at $137.01 based on Mylan's close of $59.57 on April 7, before Mylan's initial offer was made. In its

rejection, Perrigo said Mylan continues to propose offers lower than the initially rejected offer (see BioCentury, April 13 & April 27).

**Phylogica Ltd.** (ASX:PYC;Xetra:PH7), Subiaco, Australia
**PhoreMost Ltd.**, Cambridge, U.K.

Business: Cancer

Phylogica granted PhoreMost non-exclusive, worldwide rights to use undisclosed Phylomer libraries to screen cancer targets and to identify and develop small molecule drug candidates against those targets. The license caps the number of similar screening deals into which Phylogica may enter during an 18-month period, which commenced April 3. Phylogica retains non-exclusive rights and an option to negotiate for exclusive rights to commercialize Phylomer peptides and targets identified by PhoreMost. Phylogica also will receive a 7.5% equity stake in PhoreMost. The companies declined to provide further terms.

**Practice Fusion Inc.**, San Francisco, Calif.
**AstraZeneca plc** (LSE:AZN;NYSE:AZN), London, U.K.

Business: Pulmonary

Practice Fusion and AstraZeneca unveiled the population health management program for patients with asthma or chronic obstructive pulmonary disease (COPD). The program identifies patients whose asthma or COPD care does not meet National Heart, Lung, and Blood Institute and Global Initiative for Chronic Obstructive Lung Disease clinical guidelines and alerts those patients' physicians using Practice Fusion's existing electronic health records platform. AZ sponsors the program, which Practice Fusion developed. The companies declined to provide financial terms.

**Prelude Corp.**, Laguna Hills, Calif.
**Rosetta Genomics Ltd.** (NASDAQ:ROSG), Rehovot, Israel

Business: Diagnostic

Rosetta Genomics acquired fellow molecular diagnostics and services company PersonalizeDx from Prelude for $2 million in cash and 500,000 Rosetta shares valued at $1.5 million based on Rosetta's close of $2.95 on April 8, before the deal was announced. Rosetta also will provide undisclosed assets and services to Prelude. PersonalizeDx markets fluorescence *in situ* hybridization (FISH) technology-based prognostic cancer tests. Rosetta recorded $1.3 million in 2014 revenue and said PersonalizeDx recorded revenues of $6.9 million in the same period.

**Quanticel Pharmaceuticals Inc.**, San Francisco, Calif.
**Celgene Corp.** (NASDAQ:CELG), Summit, N.J.

Business: Cancer

Celgene exercised its option to acquire Quanticel for $100 million up front and up to $385 million in regulatory and development milestones. Celgene gains Quanticel's platform to perform single-cell genomic analysis of tumors along with preclinical oncology candidates that target undisclosed epigenetic modifiers. Multiple candidates from Quanticel's pipeline are due to enter clinical testing in early 2016. The acquisition is slated to close this year. Celgene received the option to acquire Quanticel under a 2011 deal, which also gave Celgene an undisclosed equity stake (see BioCentury, Nov. 7, 2011).

**Ranbaxy Laboratories Ltd.**, Gurgaon, India
**Sun Pharmaceutical Industries Ltd.** (BSE:524715;NSE:SUNPHARMA), Mumbai, India

Business: Generics

Sun completed its acquisition of Ranbaxy. Ranbaxy shareholders will receive 0.8 shares of Sun for every share of Ranbaxy held. The transaction values Ranbaxy at Rs352.5 billion ($5.5 billion) based on Sun's close of Rs1039.85 on March 24 on BSE, before the close was announced, and 423.8 million Ranbaxy shares outstanding at March 24, 2014 (see BioCentury, April 14, 2014).

**Resverlogix Corp.** (TSX:RVX), Calgary, Alberta
**Shenzhen Hepalink Pharmaceutical Co. Ltd.** (SZSE:002399), Shenzhen, China

Business: Neurology, Cardiovascular, Renal

The companies reached a framework under which Resverlogix will grant Hepalink exclusive rights to develop and commercialize RVX-208 in Taiwan and China, including Hong Kong and Macau. Resverlogix agreed not to negotiate RVX-208 licensing agreements in the territory for three months. The deal is expected to close in June.

Hepalink will receive a C$35 million ($28.7 million) equity stake in Resverlogix through the purchase of 13.3 million shares and 1 million warrants at C$2.67 per unit. Resverlogix is eligible for more than $400 million in sales milestones and single-digit royalties from Hepalink. Hepalink will be responsible for development costs in the regions. Subject to the completion of the transaction, shareholder Eastern Capital Ltd. will receive an additional C$15 million ($12.3 million) equity stake in Resverlogix through the purchase of shares and warrants at C$2.67.

Next half, Resverlogix plans to begin a Phase III trial of the inhibitor of the BET family of bromodomain-containing proteins, including bromodomain containing 4 (BRD4), to treat cardiovascular disease in patients with diabetes and low HDL. The company plans to complete regulatory submissions by 2020 for RVX-208 in China to reduce major adverse cardiac events (MACE) in diabetes patients. RVX-208 also is in development for chronic kidney disease (CKD), Alzheimer's disease (AD) and an undisclosed Orphan indication. Hepalink also will have an option to manufacture and distribute RVX-208 products outside of the four regions.

Resverlogix will have the right to select a third party to manufacture RVX-208 outside of the four regions if Hepalink fails to meet

required industry standards. The license will expire in each region 15 years after the first commercial sale of a licensed product in that region. Hepalink agreed to price RVX-208 at 110% of the manufacturing cost. Hepalink also will be entitled to nominate a representative for election to Resverlogix's board.

**RXi Pharmaceuticals Corp.** (NASDAQ:RXII), Westborough, Mass.
**MirImmune LLC**, Cambridge, Mass.

Business: Cancer

RXi granted MirImmune an exclusive license to use RNAi delivering technology, sd-rxRNA and rxRNAori, to develop cell-based cancer immunotherapies. MirImmune is responsible for R&D, manufacturing, regulatory approval and commercialization. MirImmune has rights to RXi's sd-rxRNA and rxRNAori for *ex vivo* modification of cells to treat cancer. RXi will receive an annual licensing fee and is eligible for clinical milestones, sublicensing income and single-digit royalties. RXi has an option to acquire a double-digit equity stake in MirImmune, which the company can exercise after undisclosed milestones are met. The companies could not provide details in time for publication.

**Taxus Cardium Pharmaceuticals Group Inc.** (OTCQB:CRXM), San Diego, Calif.
**Dr. Reddy's Laboratories Ltd.** (NYSE:RDY), Hyderabad, India

Business: Cardiovascular

Taxus granted Dr. Reddy's exclusive rights to co-develop and commercialize Generx cardionovo alferminogene tadenovec in the Commonwealth of Independent States (CIS), Venezuela, Vietnam and Myanmar. Dr. Reddy's also has the right of first refusal for additional exclusive licenses to commercialize Generx in over 30 other countries in Latin America and Southeast Asia. The adenoviral vector carrying the fibroblast growth factor 4 (FGF4) gene is in Phase III testing to treat refractory angina and myocardial ischemia due to advanced coronary artery disease (CAD). Dr. Reddy's declined to disclose additional details, and Taxus did not respond to inquiries.

**University of Michigan**, Ann Arbor, Mich.
**Kura Oncology Inc.**, La Jolla, Calif.

Business: Cancer

Last December, the university granted Kura exclusive, worldwide rights to a class of preclinical small molecule inhibitors targeting menin-MLL fusion oncogene, including MI-463 and MI-503. Preclinical data published in *Cancer Cell* and *Nature Medicine* showed that MI-463 and MI-503 block progression of mixed lineage acute leukemias and castration-resistant prostate cancer (CRPC) in mice.

The university will receive annual maintenance fees and up to $2.7 million in R&D funding over a three-year period. The university is eligible for undisclosed development and sales milestones. Since 2009, The Leukemia & Lymphoma Society (White Plains, N.Y.) has funded the menin-MLL fusion oncogene inhibitor program at the university under its Therapy Acceleration Program (TAP). Earlier this year, Kura disclosed the program after it reverse-merged with Zeta Acquisition Corp. III (see BioCentury, March 16).

**Vernalis plc** (LSE:VER), Winnersh, U.K.
**Taisho Pharmaceutical Holdings Co. Ltd.** (Tokyo:4581), Tokyo, Japan

Business: Infectious

Under an exclusive deal, the companies will develop antibiotics against an undisclosed target using Vernalis' fragment and structure-based drug discovery platform. Vernalis declined to provide further details, and Taisho could not be reached.

**Wellcome Trust**, London, U.K.
**Oxford Gene Technology**, Oxford, U.K.

Business: Microarrays

Wellcome Trust's Sanger Institute granted Oxford Gene Technology non-exclusive, worldwide rights to data from the Deciphering Developmental Disorders study. Oxford plans to use the data to further develop its CytoSure Constitutional v3 range of arrays to identify rare genetic diseases in research use only settings. Oxford said the study screened over 12,000 individuals with developmental disorders, uncovering potential new areas of the genome responsible for genetic disease. The partners declined to disclose financial terms.

**WuXi PharmaTech Inc.** (NYSE:WX), Shanghai, China

Business: Supply/Service

WuXi's Chairman and CEO Ge Li and Ally Bridge Group proposed to take the R&D and manufacturing services company private for $46 per ADS, or $3.3 billion. The price represents a 16% premium to WuXi's close of $39.50 on April 29, the day before the deal was announced. Li held a 1.4% stake in WuXi as of April 3. Principal shareholders listed in the filing included FIL Ltd. with 10%, Schroder Investment Management North America with 9.2% and Wellington Management Group with 7.5%. WuXi's board will form a special committee to consider the offer.

COMPANY NEWS

## SALES & MARKETING

**Basilea Pharmaceutica AG** (SIX:BSLN), Basel, Switzerland
**Astellas Pharma Inc.** (Tokyo:4503), Tokyo, Japan

Business: Infectious

Astellas launched Cresemba isavuconazonium in the U.S. to treat invasive aspergillosis and mucormycosis in adults. In March, FDA approved IV and oral formulations of the prodrug of isavuconazole, a broad-spectrum water-soluble azole antifungal. The recommended

maintenance dose for both IV and oral Cresemba is 372 mg once daily. The wholesale acquisition cost (WAC) for a single 372 mg vial of IV Cresemba is $238.50. The WAC for a seven-day supply of oral capsules is $980, or $140 per day. Astellas and Basilea are co-developing and commercializing isavuconazonium outside Japan under an amended 2010 deal (see BioCentury, March 1, 2010 & March 3, 2014).

**Courtagen Life Sciences Inc.**, Woburn, Mass.

Business: Diagnostic

Courtagen launched lysoSEEK, a genetic test that identifies enzymatic deficiencies in 94 genes associated with lysosomal storage disorders from a saliva sample.

**Gilead Sciences Inc.** (NASDAQ:GILD), Foster City, Calif.

Business: Infectious

Gilead said that Harvoni ledipasvir/sofosbuvir will now be reimbursed by provincial drug programs in Canadian provinces and territories, excluding Quebec, Prince Edward Island and Newfoundland to treat HCV genotype 1 infection. The biotech said it is working with the remaining provinces to finalize coverage. Harvoni is a fixed-dose combination of HCV drug Sovaldi sofosbuvir, a nucleotide analog HCV NS5B polymerase inhibitor, and ledipasvir, an HCV NS5A protein inhibitor. The provincial programs will reimburse the drug at the list price, which is C$22,333 ($18,300.93). Gilead's Sovaldi is reimbursed in all provincial and territorial drug programs outside of Prince Edward Island.

**Intas Pharmaceuticals Ltd.**, Ahmedabad, India

Business: Autoimmune, Biosimilars

Intas launched Intacept, a biosimilar of autoimmune Enbrel entanercept, in India. Intas says that Intracept cuts the cost of treatment "to about half" compared to Enbrel from Amgen Inc. (NASDAQ:AMGN, Thousand Oaks, Calif.).

**Pathway Genomics Corp.**, San Diego, Calif.

Business: Diagnostic

Pathway launched cancer tests ColoTrue and LynchSyndromeTrue. ColoTrue detects pathogenic variants in 15 genes associated with colorectal cancer. LynchSyndromeTrue tests five genes associated with Lynch syndrome.

**Rosetta Genomics Ltd.** (NASDAQ:ROSG), Rehovot, Israel
**Admera Health**, South Plainfield, N.J.

Business: Cancer

Rosetta launched Admera's laboratory developed test (LDT), OncoGxOne to detects alterations in 64 genes implicated in cancer and chemotherapy. Rosetta has rights to the test under a 2014 deal.

COMPANY NEWS

## OTHER NEWS

**AOP Orphan Pharmaceuticals AG**, Vienna, Austria
**Rigi Healthcare AG**, Kuessnacht, Switzerland

Business: Pharmaceuticals

AOP and Rigi Healthcare created newco Rigi Orphan Inc. USA to in-license, develop and commercialize products for rare diseases in North America. The newco will also build commercial operations to promote AOP's Orphan products in the U.S. and is in the process of complementing AOP's portfolio with additional pipeline products. The partners could not be reached for details.

**Depomed Inc.** (NASDAQ:DEPO), Newark, Calif.
**Actavis plc** (NYSE:ACT), Dublin, Ireland

Business: Neurology

The companies resolved patent litigation related to Depomed's Gralise gabapentin. Under the settlement, Actavis admits that all seven patents owned by Depomed covering Gralise are valid and enforceable and would be infringed by Actavis' proposed generic. The patents expire between 2016 and February 2024, but Depomed granted Actavis a license to launch a generic in the U.S. by Jan. 1, 2024. The settlement resolves Actavis' pending appeal filed in the U.S. Court of Appeals for the Federal Circuit after the U.S. District Court for the District of New Jersey ruled in favor of Depomed (see BioCentury, Sept. 8, 2014).

The once-daily formulation of gabapentin using Acuform delivery technology is marketed as an Orphan drug in the U.S. to manage postherpetic neuralgia (PHN). Depomed reported 2014 worldwide sales of $60.4 million for Gralise.

**The Medicines Co.** (NASDAQ:MDCO), Parsippany, N.J.
**Sun Pharmaceutical Industries Ltd.** (BSE:524715; NSE:SUNPHARMA), Mumbai, India

Business: Cardiovascular

The companies resolved patent litigation related to anticoagulant Angiomax bivalirudin from The Medicines Co. Under the settlement, Sun Pharmaceuticals admits that U.S. Patent Nos. 7,582,727 and 7,598,343 covering the small molecule direct thrombin inhibitor are valid and enforceable and would be infringed by Sun's proposed generic. The patents expire on July 27, 2028, but Medicines Co. granted Sun a license to launch a generic in the U.S. by June 30, 2019. The settlement resolves a lawsuit filed in the U.S. District Court for the District of New Jersey. Medicines Co. reported 2014 U.S. sales of $599.5 million for Angiomax.

**Pacira Pharmaceuticals Inc.** (NASDAQ:PCRX), Parsippany, N.J.

Business: Neurology

Pacira said it received a subpoena from the U.S. Department of Justice, U.S. Attorney's Office for the District of New Jersey, requesting documents related to marketing and promotional practices for Exparel. Pacira markets the bupivacaine liposome extended-release injectable suspension using DepoFoam drug delivery technology for postoperative pain management. The company reported $188.5 million in 2014 net sales for Exparel.

CLINICAL NEWS

## REGULATORY

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

Product: Botox onabotulinumtoxinA (formerly botulinum toxin)
Business: Musculoskeletal

FDA approved an sBLA for Botox onabotulinumtoxinA from Actavis to treat upper limb spasticity that expands the label for the indication to include 2 additional thumb muscles — flexor pollicis longus and adductor pollicis. The approval also increases the maximum dose to 400 units from 360 in upper limb spasticity. Actavis gained the vacuum-dried purified botulinum toxin type A through its March acquisition of Allergan Inc. (see BioCentury, March 23).

Botox is marketed in the U.S. for various indications, including overactive bladder (OAB), urinary incontinence, upper limb spasticity, chronic migraines, cervical dystonia, severe axillary hyperhidrosis, blepharospasm and strabismus.

**Array BioPharma Inc.** (NASDAQ:ARRY), Boulder, Colo.
**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.

Product: Selumetinib (ARRY-886, AZD6244)
Business: Cancer

FDA granted Orphan Drug designation to selumetinib from AstraZeneca to treat uveal melanoma. The small molecule MEK inhibitor is in Phase III testing for first-line treatment of metastatic uveal melanoma in combination with chemotherapy, with data expected this year. In 2003, Array granted AZ rights to selumetinib for oncology indications (see BioCentury, Dec. 22, 2003).

**Array BioPharma Inc.** (NASDAQ:ARRY), Boulder, Colo.
**VentiRx Pharmaceuticals Inc.**, Seattle, Wash.

Product: Motolimod (VTX-2337)
Business: Cancer

The European Commission granted Orphan Drug designation to VentiRx's motolimod to treat ovarian cancer. The small molecule toll-like receptor 8 (TLR8) agonist is in Phase II testing to treat ovarian cancer in patients whose disease has progressed on or recurred after platinum-based chemotherapy. Data are expected early next year. The product has Fast Track and Orphan Drug designations in the U.S. to treat ovarian cancer.

Motolimod is also in Phase II testing to treat squamous cell carcinoma of the head and neck (SCCHN). VentiRx has exclusive, worldwide rights to the compound from Array BioPharma under a 2007 deal (see BioCentury, March 19, 2007). Celgene Corp. (NASDAQ:CELG, Summit, N.J.) has an exclusive option to acquire VentiRx following Phase II data of motolimod in ovarian or head and neck cancer (see BioCentury, Oct. 8, 2012).

**Arrowhead Research Corp.** (NASDAQ:ARWR), Pasadena, Calif.
**Calando Pharmaceuticals Inc.**, Pasadena, Calif.
**Cerulean Pharma Inc.** (NASDAQ:CERU), Cambridge, Mass.

Product: CRLX101 (formerly IT-101)
Business: Cancer

FDA granted Fast Track designation to Cerulean's CRLX101 to treat metastatic renal cell carcinoma (RCC) in combination with Avastin bevacizumab following progression through 2-3 prior lines of therapy. CRLX101, a dual inhibitor of topoisomerase I (TOP1) and hypoxia-inducible factor 1 alpha (HIF1A; HIF1-alpha) is in a Phase II trial in combination with Avastin for relapsed RCC. Cerulean has exclusive, worldwide rights to develop and commercialize CRLX101 from Calando, a subsidiary of Arrowhead (see BioCentury, June 29, 2009).

**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.

Product: Tremelimumab (CP-675,206, CP-675206, CP-675)
Business: Cancer

FDA granted Orphan Drug designation to tremelimumab from AstraZeneca to treat malignant mesothelioma. The human mAb against CTLA-4 (CD152) is in a pivotal Phase II trial for second-line treatment of pleural or peritoneal malignant mesothelioma, with data expected this year. AZ's MedImmune LLC unit has worldwide rights to tremelimumab from Pfizer (see BioCentury, Oct. 10, 2011).

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

Product: Brilinta ticagrelor (Brilique–EU) (AZD6140)
Business: Cardiovascular

FDA accepted and granted Priority Review to an sNDA for Brilinta ticagrelor to prevent major cardiovascular thrombotic events in patients with a history of myocardial infarction (MI). The PDUFA date is next quarter; a specific date was not disclosed. The application is based on data from the double-blind, international Phase III PEGASUS-TIMI 54 trial in >21,000 patients who had experienced a heart attack 1-3 years prior to the start of the study and who had 1 additional cardiovascular risk factor (see BioCentury, Jan. 19).

Brilinta is marketed to reduce the rate of cardiovascular thrombotic events in patients with acute coronary syndrome (ACS), including unstable angina, ST-elevation myocardial infarction (STEMI) and non-STEMI. The purinergic receptor P2Y G protein-coupled 12 (P2RY12; P2Y12) antagonist is approved as Brilique in the EU.

**aTyr Pharma Inc.**, San Diego, Calif.

Product: Resokine, Resolaris
Business: Musculoskeletal

FDA granted Orphan Drug designation to Resolaris from aTyr to treat facioscapulohumeral muscular dystrophy (FSHD). Resolaris is in a European Phase Ib/II trial for FSHD. The protein therapy is

based on non-canonical functions of secreted forms of aminoacyl tRNA synthetases.

**Bio-Path Holdings Inc.** (NASDAQ:BPTH), Houston, Texas

Product: Liposomal Grb-2 (BP-100-1.01)
Business: Cancer

FDA granted Orphan Drug designation to Liposomal Grb-2 from Bio-Path to treat acute myelogenous leukemia (AML). The liposomal antisense inhibitor of growth factor receptor-bound protein 2 (GRB2) expression is in Phase II testing for AML, with data expected next half.

**BioBlast Pharma Ltd.** (NASDAQ:ORPN), Tel Aviv, Israel

Product: Cabaletta
Business: Musculoskeletal

FDA granted Fast Track designation to Cabaletta from BioBlast to treat oculopharyngeal muscular dystrophy (OPMD). The compound is in the Phase II/III HOPE trial for OPMD, for which it has Orphan Drug designation. Cabaletta is an IV solution of the disaccharide trehalose, which reduces the pathological aggregation of proteins within cells.

**Biogen Inc.** (NASDAQ:BIIB), Cambridge, Mass.
**AbbVie Inc.** (NYSE:ABBV), Chicago, Ill.

Product: Zinbryta daclizumab high-yield process (DAC HYP)
Business: Autoimmune

FDA accepted for review a BLA from Biogen and AbbVie for Zinbryta daclizumab high-yield process to treat relapsing forms of multiple sclerosis. The companies are developing and commercializing the humanized mAb against IL-2 receptor alpha chain (CD25) for MS. In March, the EMA accepted for review an MAA from Biogen and AbbVie for Zinbryta (see BioCentury, April 13).

**BioMarin Pharmaceutical Inc.** (NASDAQ:BMRN), Novato, Calif.

Product: Drisapersen (2402968) (PRO051, GSK2402968)
Business: Musculoskeletal

BioMarin completed submission of a rolling NDA to FDA for drisapersen to treat Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping. The antisense oligoribonucleotide that induces exon 51 skipping on the dystrophin gene has Fast Track, Orphan Drug and breakthrough therapy designation in the U.S. for DMD. BioMarin said that in about 13% of DMD patients, skipping of exon 51 restores the proper dystrophin reading frame.

BioMarin plans to submit an MAA to EMA for conditional approval of drisapersen this summer. The company gained the product through its acquisition of Prosensa Holding N.V. last quarter.

**Boehringer Ingelheim GmbH**, Ingelheim, Germany

Product: Idarucizumab (dabigatran antidote) (BI 655075)
Business: Hematology

FDA accepted and granted Priority Review to a BLA from Boehringer seeking accelerated approval of idarucizumab to reverse the anticoagulant effects of Pradaxa dabigatran etexilate mesylate. Idarucizumab, a Fab fragment against dabigatran, has breakthrough therapy designation in the U.S. (see BioCentury, March 9). Boehringer has submitted regulatory applications in the EU and Canada (see BioCentury, March 23). Boehringer markets Pradaxa, a direct oral thrombin inhibitor.

**Capricor Therapeutics Inc.** (NASDAQ:CAPR), Beverly Hills, Calif.
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

Product: CAP-1002
Business: Cardiovascular

FDA granted Orphan Drug designation to CAP-1002 from Capricor to treat cardiomyopathy associated with Duchenne muscular dystrophy (DMD). The allogeneic cardiosphere-derived stem cell therapy is in Phase I/II testing to treat myocardial infarction (MI) and Phase I testing to treat advance heart failure.

Johnson & Johnson's Janssen Biotech Inc. unit has an exclusive option from Capricor to license worldwide rights to CAP-1002. Capricor is also partnered with Janssen to develop Capricor's cell therapy programs for cardiologic applications, including CAP-1002 (see BioCentury, Aug. 11, 2014).

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

Product: Pomalyst pomalidomide (Imnovid–EU) (CC-4047)
Business: Cancer

FDA approved an updated label for Pomalyst pomalidomide from Celgene to include progression-free survival (PFS) and overall survival (OS) benefits for patients with refractory multiple myeloma (MM). Celgene said it fulfilled FDA's accelerated approval requirements based on data from the Phase III MM-003 trial. Pomalyst is approved in the U.S. to treat MM in combination with dexamethasone in patients who have received at least 2 prior therapies, including Revlimid lenalidomide and a proteasome inhibitor, and have demonstrated disease progression on or within 60 days of completion of the last therapy (see BioCentury, Feb. 11, 2013).

In 2013, FDA granted accelerated approval to the thalidomide analog based on response rates from the Phase II portion of the Phase I/II MM-002 trial. Final data from MM-002 showed that Pomalyst plus low-dose dexamethasone led to median PFS, the primary endpoint, of 3.6 months vs. 1.8 months for high-dose dexamethasone ($p<0.001$). The Pomalyst arm also led to a median OS of 12.4 months vs. 8 months for high-dose dexamethasone ($p=0.009$).

**Cepheid Inc.** (NASDAQ:CPHD), Sunnyvale, Calif.

Product: Xpert HCV Viral Load
Business: Diagnostic

Cepheid received CE Mark approval for Xpert HCV Viral Load test as an aid in managing HCV-infected patients undergoing antiviral therapy and for confirmation of HCV serologic test results. The company plans to launch the *in vitro* quantitative diagnostic that detects HCV RNA this month. The test runs on Cepheid's GeneXpert System.

**Daiichi Sankyo Co. Ltd.** (Tokyo:4568), Tokyo, Japan

Product: Savaysa edoxaban (Lixiana) (DU-176b)
Business: Cardiovascular

EMA's CHMP recommended approval of Lixiana edoxaban from Daiichi Sankyo to prevent stroke and systemic embolism in adults with non-valvular atrial fibrillation (AF); treat deep vein thrombosis (DVT) and pulmonary embolism (PE); and prevent recurrent DVT and PE. The oral Factor Xa inhibitor is approved in the U.S., Japan and Switzerland.

**Eiger Biopharmaceuticals Inc.**, San Carlos, Calif.
**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.

Product: Lonafarnib (MK-6336) (formerly SCH 066336)
Business: Infectious

FDA granted Fast Track designation to lonafarnib from Eiger to treat HDV infection in combination with ritonavir. The farnesyl transferase inhibitor is in Phase II testing for the indication, for which the product also has Orphan Drug designation in the U.S. and EU. In 2010, Eiger gained exclusive, worldwide rights to lonafarnib from Merck.

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

Product: Cyramza ramucirumab (LY3009806, IMC-1121B)
Business: Cancer

FDA approved an sBLA from Eli Lilly for Cyramza ramucirumab to treat metastatic colorectal cancer (mCRC) in combination with FOLFIRI therapy in patients with disease progression on or after prior therapy with Avastin bevacizumab, oxaliplatin and a fluoropyrimidine. The label includes an updated black box warning of gastrointestinal perforation and impaired wound healing and an increased risk of gastrointestinal hemorrhage. The black box already had a warning for an increased risk of hemorrhage. The human IgG1 mAb VEGF receptor 2 (KDR/Flk-1; VEGFR-2) antagonist is approved for gastric and non-small cell lung cancer (NSCLC).

**Emergent BioSolutions Inc.** (NYSE:EBS), Rockville, Md.

Product: Ixinity trenonacog alfa (IB1001)
Business: Hematology

FDA approved a BLA for Ixinity trenonacog alfa from Emergent to control and prevent bleeding episodes and for perioperative management in patients ages ≥12 with hemophilia B. The company plans to launch the recombinant coagulation Factor IX (rFIX) this quarter.

**Enanta Pharmaceuticals Inc.** (NASDAQ:ENTA), Watertown, Mass.
**AbbVie Inc.** (NYSE:ABBV), Chicago, Ill.

Product: Viekirax ombitasvir/paritaprevir/ritonavir
Business: Infectious

FDA accepted and granted Priority Review to an NDA from AbbVie for an all-oral, once-daily, interferon-free treatment of ombitasvir/paritaprevir/ritonavir with ribavirin to treat chronic HCV genotype 4 infection. AbbVie expects a decision from the agency next quarter. Japan's Ministry of Health, Labor and Welfare (MHLW) also accepted and granted Priority Review to an NDA for ombitasvir/paritaprevir/ritonavir to treat chronic HCV genotype 1 infection. The product is a combination of paritaprevir, an HCV NS3/4A protease inhibitor, plus booster Norvir ritonavir and ombitasvir, an HCV NS5A protein inhibitor. AbbVie markets Norvir, an HIV protease inhibitor. Paritaprevir is partnered with Enanta.

In the EU, ombitasvir/paritaprevir/ritonavir is approved as Viekirax in combination with AbbVie's Exviera dasabuvir for HCV infection. In the U.S., Viekirax and Exviera are co-packaged and marketed as Viekira Pak. Exviera is a non-nucleoside HCV NS5B polymerase inhibitor.

**Exelixis Inc.** (NASDAQ:EXEL), South San Francisco, Calif.

Product: Cometriq cabozantinib (XL184)
Business: Cancer

FDA granted Fast Track designation to Cometriq cabozantinib from Exelixis to treat advanced renal cell carcinoma (RCC) in patients who received 1 prior therapy. The spectrum-selective kinase inhibitor of VEGF receptor 2 (KDR/Flk-1; VEGFR-2) and c-Met receptor tyrosine kinase is in the Phase III METEOR trial to treat metastatic RCC. Top-line data are expected this quarter.

Exelixis markets Cometriq in the U.S. to treat progressive, metastatic medullary thyroid cancer (MTC). The product has conditional approval for MTC in the EU.

**Great Basin Corp.** (NASDAQ:GBSN), Salt Lake City, Utah

Product: Portrait GBS Assay
Business: Diagnostic

FDA granted 510(k) clearance for Great Basin's Portrait GBS Assay to detect group B *Streptococcus* infection from rectovaginal swabs. Great Basin plans to launch the assay in the U.S. this quarter. The automated assay runs on the Portrait instrument and employs hot-start PCR to amplify the group B *Streptococcus* cfb gene using biotin-labeled primers followed by hybridization and detection.

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

Product: Cannabidiol (IV GWP42003)
Business: Neurology

FDA granted Orphan Drug designation to IV GWP42003 from GW to treat neonatal hypoxic-ischemic encephalopathy. Next half, the company plans to start a Phase I trial of the IV cannabidiol, a phytocannabinoid found in *Cannabis sativa*.

**Hapten Pharmaceuticals LLC**, New York, N.Y.

**RXi Pharmaceuticals Corp.** (NASDAQ:RXII), Westborough, Mass.

Product: Samcyprone
Business: Cancer

FDA granted Orphan Drug designation to Samcyprone from RXi to treat stage IIB-IV malignant melanoma. The gel formulation of diphenylcyclopropenone (DPCP), which initiates a T cell response by altering the expression of multiple genes and miRNAs, is in Phase IIa testing for cutaneous metastases of melanoma. RXi has exclusive, worldwide rights from Hapten to develop and commercialize Samcyprone to treat dermatological diseases.

**Kythera Biopharmaceuticals Inc.** (NASDAQ:KYTH), Calabasas, Calif.

Product: Kybella deoxycholic acid (ATX-101)
Business: Other

FDA approved an NDA from Kythera for Kybella deoxycholic acid to improve the appearance of moderate to severe convexity or fullness associated with submental (under chin) fat. Kythera expects to begin training physicians in June on the safe use of Kybella before sales begin. The company has submitted regulatory applications for the synthetic sodium deoxycholate in Canada, Switzerland and Australia.

**Medicure Inc.** (TSX-V:MPH; OTCQB:MCUJF), Winnipeg, Manitoba

**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.

Product: Aggrastat tirofiban
Business: Cardiovascular

FDA approved a label revision for cardiovascular drug Aggrastat tirofiban from Medicure to amend the dosing time for the 25 µg/kg high-dose bolus regimen to "within 5 minutes" from "over 3 minutes" in patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS). The maintenance dose is unchanged at 0.15 µg/kg/min. The non-peptide Integrin alpha(2b)beta(3) (GPIIb/IIIa; CD41/CD61) antagonist is approved in the U.S. to reduce the rate of thrombotic cardiovascular events in patients with NSTE-ACS. Medicure has U.S. rights to the product from Merck.

**Medivation Inc.** (NASDAQ:MDVN), San Francisco, Calif.

**Astellas Pharma Inc.** (Tokyo:4503), Tokyo, Japan

Product: Xtandi enzalutamide (formerly MDV3100)
Business: Cancer

Health Canada approved an sNDS from Astellas for Xtandi enzalutamide to treat metastatic castration-resistant prostate cancer (CRPC) in patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy. The once-daily oral androgen receptor antagonist is also approved in Canada to treat metastatic CRPC in patients who previously received docetaxel in the setting of medical or surgical castration. Medivation and Astellas partnered to develop and commercialize Xtandi in 2009 (see BioCentury, Nov. 2, 2009).

**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.

Product: Bridion sugammadex (MK-8616) (formerly Org 25969, SCH 900616)
Business: Neurology

FDA issued a complete response letter to Merck for an NDA for sugammadex to reverse neuromuscular blockade due to muscle relaxants rocuronium or vecuronium. Merck said FDA asked for additional sensitivity analyses regarding the data the pharma had submitted. Merck expects to respond to the agency "in the very near future." Last month, FDA cancelled an advisory committee meeting to discuss sugammadex and Merck said it expected the agency to issue a complete response letter (see BioCentury, March 30).

FDA issued a not approvable letter for sugammadex in 2008 due to issues "primarily related to hypersensitivity/allergic reactions," and issued a complete response letter in 2013 due to concerns about the "operational aspects" of a hypersensitivity study the agency requested (see BioCentury, Sept. 30, 2013). Merck's U.S. patent for sugammadex expires in 2021. The pharma markets the cyclodextrin derivative as Bridion outside the U.S.

**Merrimack Pharmaceuticals Inc.** (NASDAQ:MACK), Cambridge, Mass.

**PharmaEngine Inc.** (GreTai:4162), Taipei, Taiwan

**Baxter International Inc.** (NYSE:BAX), Deerfield, Ill.

Product: Irinotecan (nal-IRI) (PEP02, MM-398)
Business: Cancer

Merrimack completed submission of a rolling NDA to FDA for MM-398 to treat metastatic adenocarcinoma of the pancreas in patients who have been previously treated with gemcitabine-based therapy. The company requested Priority Review for the application. The nanoparticle liposome formulation of irinotecan has Fast Track designation in the U.S. and Orphan Drug designation in the U.S. and EU for pancreatic cancer.

Merrimack has exclusive, worldwide rights to MM-398 from PharmaEngine outside of Taiwan, where PharmaEngine retains rights. Baxter has exclusive rights from Merrimack to the compound outside of the U.S. and Taiwan (see BioCentury, Sept. 29, 2014).

**Nektar Therapeutics** (NASDAQ:NKTR), San Francisco, Calif.
**Baxter International Inc.** (NYSE:BAX), Deerfield, Ill.

Product: BAX 855
Business: Hematology

Baxter submitted an NDA in Japan for BAX 855 to treat hemophilia A in patients ages ≥12. In December, the company submitted a BLA to FDA for the pegylated form of recombinant Factor VIII. Baxter plans to submit an MAA to EMA next year. BAX 855 uses PEGylation technology from Nektar, which partnered with Baxter to develop a pegylated form of hemophilia A drug Advate recombinant Factor VIII from Baxter (see BioCentury, Oct. 3, 2005 & Dec. 24, 2007).

**NeoStem Inc.** (NASDAQ:NBS), New York, N.Y.

Product: Melapuldencel-T (TC-DC, Tumor Stem Cell Specific Dendritic Cell therapy, DC-TC) (NBS20) (formerly NBS-20)
Business: Cancer

EMA classified NeoStem's NBS20 as an advanced therapy medicinal product (ATMP). The tumor cell-specific dendritic cell therapy is in the Phase III Intus trial to treat recurrent stage III or IV metastatic melanoma. NBS20 has Orphan Drug and Fast Track designation in the U.S. to treat metastatic melanoma.

**Novogen Ltd.** (ASX:NRT; NASDAQ:NVGN), Hornsby, Australia

Product: Cantrixil
Business: Cancer

FDA granted Orphan Drug designation to Novogen's Cantrixil to treat ovarian cancer. Cantrixil is a cyclodextrin envelope containing cytotoxic TRXE-002, a dimer of 2 benzopyran rings called a super-benzopyran, designed for intra-peritoneal use. It is slated to enter Phase I testing in late 2015 or early 2016 to treat malignant ascites. In 2013, Novogen and Yale University (New Haven, Conn.) formed a JV, CanTx Inc. (New Haven, Conn.), to develop personalized approaches to chemotherapy to treat ovarian cancer (see BioCentury, Nov. 11, 2013). Novogen licensed TRXE-002 to CanTx for use in Cantrixil.

**Oasmia Pharmaceutical AB** (SSE:OASM A), Uppsala, Sweden

Product: Micellular paclitaxel (Paclical) (OAS-PAC-100)
Business: Cancer

Russia approved Paclical micellular paclitaxel from Oasmia to treat epithelial ovarian cancer in combination with carboplatin. Oasmia said a launch of the water-soluble formulation of paclitaxel is slated for 2H15. Pharmasyntez (Irkutsk, Russia) has exclusive commercialization and distribution rights in the Commonwealth of Independent States (CIS) (see BioCentury, Feb. 11, 2013).

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

Product: Reolysin pelareorep
Business: Cancer

FDA granted Orphan Drug designation to Reolysin from Oncolytics to treat malignant glioma. The formulation of human reovirus type 3, an oncolytic virus, has completed Phase I/II trials for recurrent malignant glioma.

**Otonomy Inc.** (NASDAQ:OTIC), San Diego, Calif.

Product: AuriPro (formerly OTO-201)
Business: Infectious

FDA accepted for review an NDA for AuriPro from Otonomy to treat middle ear effusion in pediatric patients undergoing tympanostomy tube placement surgery. The PDUFA date is expected to be in late December. Otonomy hopes to market the sustained-release gel formulation of ciprofloxacin in 1Q16.

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

Product: Abilify aripiprazole
Business: Neurology

FDA approved ANDAs from multiple companies for generic versions of Otsuka's Abilify aripiprazole to treat schizophrenia and bipolar disorder. Abilify is a small molecule partial agonist of the dopamine D2 and serotonin (5-HT1A) receptors and antagonist of the serotonin (5-HT2A) receptor.

In March, Otsuka filed a suit in the U.S. District Court for the District of Maryland alleging that FDA unlawfully broadened the approved indication for Abilify. Otsuka said it submitted an sNDA to expand Abilify's label to include pediatric Tourette's syndrome, but FDA broadened the approved indication to "patients with Tourette's Disorder." The broadened indication would disqualify the drug for Orphan Drug exclusivity (see BioCentury, April 13).

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

Product: Xalkori crizotinib (PF-02341066)
Business: Cancer

FDA granted breakthrough therapy designation to Xalkori crizotinib to treat c-ros proto-oncogene 1 receptor tyrosine kinase (ROS1)-positive non-small cell lung cancer (NSCLC). The designation is based on data from an expansion cohort of the international Phase I Study 1001, which evaluated the product in 50 patients with ROS1-positive advanced NSCLC. Pfizer markets the dual inhibitor of c-Met receptor tyrosine kinase and anaplastic lymphoma kinase (ALK) and their oncogenic variants in the U.S. to treat ALK-positive NSCLC.

**Quest Diagnostics Inc.** (NYSE:DGX), Madison, N.J.
**3M Co.** (NYSE:MMM), St. Paul, Minn.

Product: Simplexa Group A Strep Direct
Business: Diagnostic

FDA granted 510(k) clearance to Simplexa Group A Strep Direct Kit from Quest to detect Group A *Streptococcus* bacteria from throat

swabs. The agency categorized it as a moderate complexity test. Quest said the real time-PCR assay for *in vitro* qualitative detection of group A *Streptococcus* DNA is available in the U.S. It has CE Mark approval and is available in Europe. The test runs on the3M Integrated Cycler co-developed by Focus and 3M (see BioCentury, Nov. 7, 2011).

**Sanofi** (Euronext:SAN; NYSE:SNY), Paris, France

Product: Toujeo insulin glargine (formerly U300)
Business: Endocrine/Metabolic

The European Commission approved once-daily Toujeo insulin glargine from Sanofi to treat Type I and Type II diabetes in adults. Earlier this year, the pharma launched the product in the U.S. to improve glycemic control in Type I and II diabetics. The product is a 300 units/mL formulation of insulin glargine, a synthetic sustained-release subcutaneous insulin analog (see BioCentury, April 6).

**Sanofi** (Euronext:SAN; NYSE:SNY), Paris, France

Product: GZ402671, GZ/SAR402671
Business: Endocrine/Metabolic

FDA granted Fast Track designation to GZ/SAR402671 from Sanofi's Genzyme Corp. company to treat Fabry's disease. The glucosylceramide synthase (GCS) inhibitor is in a Phase IIa trial for the indication.

**Seattle Genetics Inc.** (NASDAQ:SGEN), Bothell, Wash.
**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502), Osaka, Japan

Product: Adcetris brentuximab vedotin (SGN-35)
Business: Cancer

FDA accepted and granted Priority Review to an sBLA for Adcetris brentuximab vedotin from Seattle Genetics as consolidation therapy immediately following an autologous stem cell transplant (ASCT) in Hodgkin's lymphoma (HL) patients at high risk of relapse. The PDUFA date is Aug. 18.

Adcetris has accelerated approval from FDA to treat HL after failure of ASCT or after failure of ≥2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates and to treat systemic anaplastic large cell lymphoma (ALCL) after failure of ≥1 prior multi-agent chemotherapy regimen. The antibody-drug conjugate (ADC) composed of an anti-CD30 mAb and monomethyl auristatin E (MMAE) also has conditional approval in the EU.

Seattle Genetics is co-developing Adcetris with Takeda's Millennium Pharmaceuticals Inc. subsidiary worldwide, except in Japan, where Millennium is responsible for development. Millennium has marketing rights outside the U.S. and Canada, where Seattle Genetics retains rights.

**Shire plc** (LSE:SHP; NASDAQ:SHPG), Dublin, Ireland
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

Product: Resolor prucalopride (SHP555) (formerly SPD 555)
Business: Gastrointestinal

EMA's CHMP recommended approval of an expanded label for Resolor prucalopride from Shire to include symptomatic treatment of chronic constipation in men in whom laxatives fail to provide adequate relief. Resolor is approved for the indication in women. Shire has U.S. and European rights to the serotonin (5-HT4) receptor agonist from Johnson & Johnson (see BioCentury, Jan. 16, 2012).

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

Product: Raplixa (formerly Fibrocaps)
Business: Hematology

FDA approved a BLA from The Medicines Co. for Raplixa fibrin sealant as adjunctive hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques is ineffective or impractical. The agency also approved the RaplixaSpray device, which is used to administer the dry powder topical fibrin sealant composed of fibrinogen and thrombin. The company plans to launch the product next quarter. The European Commission approved Raplixa in late March.

**Theravance Inc.** (NASDAQ:THRX), South San Francisco, Calif.
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.

Product: Breo Ellipta fluticasone furoate/vilanterol (Relvar) (GW685698/GW64244) (formerly Relovair)
Business: Inflammation

FDA approved an sNDA for Breo Ellipta fluticasone furoate/vilanterol from GlaxoSmithKline and Theravance as a once-daily maintenance treatment for asthma in adults. The agency issued a complete response letter for the product's use in patients aged 12-17. According to the partners, FDA requested additional data in the age group. Breo Ellipta is approved in the U.S. for maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). The product is a fixed-dose combination of the inhaled corticosteroid fluticasone furoate and the long-acting adrenergic receptor beta 2 agonist (LABA) vilanterol administered with the dry powder Ellipta inhaler.

In March, FDA's Pulmonary-Allergy Drugs and Drug Safety and Risk Management advisory committees voted 16-4 to recommend Breo Ellipta in adults, but 18-2 against approval in children ages 12-17 (see BioCentury, March 23). Theravance manages royalty streams for programs partnered with GSK.

CLINICAL NEWS

## CLINICAL RESULTS

**AmpliPhi Biosciences Corp.** (OTCBB:APHB), Richmond, Va.
**Celladon Corp.** (NASDAQ:CLDN), San Diego, Calif.

Product: AAV1/SERCA2a (Mydicar)
Business: Cardiovascular
Molecular target: ATPase Ca++ transporting cardiac muscle slow twitch 2 (ATP2A2) (SERCA2A)
Description: Recombinant adeno-associated viral (AAV) vector bearing the gene for ATPase Ca++ transporting cardiac muscle slow twitch 2 (ATP2A2; SERCA2A), which is found in the sarcoplasmic reticulum
Indication: Treat advanced heart failure
Endpoint: Time to recurrent heart failure-related events, defined as heart failure-related hospitalizations or ambulatory treatment for worsening heart failure; time to first terminal event, defined as all-cause death, heart transplant or need for placement of a mechanical circulatory support device, and safety
Status: Phase IIb data
Milestone: NA

The double-blind, international Phase IIb CUPID 2 trial in 243 evaluable patients with stable NYHA class II to IV heart failure showed that a single intracoronary infusion of Mydicar missed the primary endpoint of reducing time to recurrent heart failure-related events, defined as heart failure-related hospitalizations or ambulatory treatment for worsening heart failure, vs. placebo (HR=0.93, 95% CI: 0.53, 1.65, p=0.81). Mydicar also missed the secondary endpoint of reducing time to first terminal event, defined as all-cause death, heart transplant or need for placement of a mechanical circulatory support device, vs. placebo. Patients also received their maximal, optimized heart failure therapy.

Mydicar is also in a Phase II trial to treat advanced heart failure in patients with left ventricular assist devices (LVAD). Celladon has exclusive rights to develop and commercialize certain AAV-based technologies from AmpliPhi Biosciences, including the technology for Mydicar (see BioCentury, March 16, 2009).

**Array BioPharma Inc.** (NASDAQ:ARRY), Boulder, Colo.
**Loxo Oncology Inc.** (NASDAQ:LOXO), Stamford, Conn.

Product: LOXO-101
Business: Cancer
Molecular target: Neurotrophic tyrosine kinase receptor 1 (TrkA) (NTRK1)
Description: Neurotrophic tyrosine kinase receptor 1 (TrkA; NTRK1) inhibitor
Indication: Treat advanced solid tumors
Endpoint: Safety and maximum tolerated dose (MTD) (Phase Ia) and overall response rate (ORR) (Phase Ib); progression-free survival (PFS) and pharmacokinetics
Status: Interim Phase Ia data
Milestone: Start Phase Ib (2H15)

Interim data from 15 patients with advanced solid tumors in the Phase Ia portion of an open-label, dose-escalation, U.S. Phase Ia/Ib trial showed that once-daily 50 and 100 mg and twice-daily 100 mg oral LOXO-101 were generally well tolerated with no treatment-related serious adverse events reported. The most common adverse events reported were grade 1/2 fatigue, dizziness and anemia. The MTD has not yet been reached. Data were presented at the American Association for Cancer Research meeting in Philadelphia. Loxo has exclusive, worldwide rights to LOXO-101 from Array.

**Biothera Inc.**, Eagan, Minn.

Product: Imprime PGG
Business: Cancer
Molecular target: Complement receptor 3 (CR3) (CD11b)
Description: Soluble beta glucan derived from the cell walls of Saccharomyces cerevisiae
Indication: Treat non-small cell lung cancer (NSCLC)
Endpoint: Objective response rate (ORR); disease control rate (DCR), complete response (CR), partial response (PR) and stable disease (SD) rates, duration of response, time to progression (TTP), overall survival (OS), progression-free survival (PFS), safety and pharmacokinetics
Status: Additional Phase II data
Milestone: Start Phase III (mid-2016)

Additional data from an open-label, international Phase II trial in 92 patients with previously untreated stage IV non-squamous NSCLC showed that once-weekly 4 mg/kg IV Imprime PGG plus Avastin bevacizumab, paclitaxel and carboplatin led to an ORR of 60.4%, including 1 CR and 28 PRs, plus 16 cases of SD vs. an ORR of 43.5%, including 10 PRs, plus 11 cases of SD for Avastin, paclitaxel and carboplatin alone (p=0.2096). Median OS was 16.1 months and median PFS was 11.9 months for the Imprime PGG arm vs. 11.6 and 10.2 months, respectively, for the control arm (p=0.1345 for OS and p=0.5901 for PFS). Median duration of response was 10.3 months for the Imprime PGG arm vs. 5.6 months for the control arm (p=0.904). Additionally, 20% of patients in the Imprime PGG arm achieved a >10 mm reduction in tumor size vs. 0% of patients in the control arm. Imprime PGG was well tolerated with chills, dyspnea, fatigue, nausea, pyrexia and infusion-related reactions reported as the most common treatment-related adverse events. Data were presented at the European Lung Cancer meeting in Geneva. Biothera previously reported interim data from the trial (see BioCentury, May 2, 2011). In mid-2016, the company plans to start a Phase III trial of Imprime PGG as first-line treatment of NSCLC.

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

Product: Daklinza daclatasvir (BMS-790052)
Business: Infectious
Molecular target: HCV NS5A protein

Description: Selective HCV NS5A protein inhibitor
Indication: Treat HCV infection in cirrhotic patients and patients with post-liver transplant HCV recurrence
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment; HCV RNA levels and safety
Status: Phase III data
Milestone: NA

The open-label, U.S. Phase III ALLY-1 trial in 113 patients with HCV infection of any genotype and with advanced cirrhosis or post-liver transplant recurrence of HCV showed that once-daily 60 mg Daklinza daclatasvir and 400 mg Sovaldi sofosbuvir plus ribavirin for 12 weeks led to an SVR 12 weeks after the end of treatment, the primary endpoint, in 83% of patients with advanced cirrhosis (n=60) and in 94% of post-liver transplant patients with HCV recurrence (n=53) and. In patients with HCV genotype 1 infection, the SVR12 rate was 82% in patients with advanced cirrhosis and 95% in post-liver transplant patients with HCV recurrence. Additionally, 97% of post-liver transplant patients with HCV genotype 1a infection and 91% of post-liver transplant patients with HCV genotype 3 infection achieved an SVR12. Furthermore, 56% of patients with decompensated cirrhosis Child-Pugh class C (n=16) achieved an SVR12.

Four advanced cirrhotic patients received a liver transplant during treatment and all 4 achieved an SVR12. One patient discontinued treatment after 31 days due to headache but still achieved an SVR12. There were 9 relapses post-treatment in the cirrhosis cohort and 1 patient had detectable HCV RNA levels at the end of treatment. There were no on-treatment virologic breakthroughs. There were 3 relapses in the post-transplantation cohort. All 12 patients who relapsed are being treated with Daklinza and Sovaldi plus ribavirin for 24 weeks. Data were presented at the European Association for the Study of the Liver meeting in Vienna.

Gilead Sciences Inc. (NASDAQ:GILD, Foster City, Calif.) markets Sovaldi, a nucleotide analog HCV NS5B polymerase inhibitor, in the U.S., EU and Canada to treat HCV infection. Daklinza is approved in the EU and Japan for HCV infection. In March, FDA accepted for review a resubmitted NDA for Daklinza in combination with Sovaldi to treat chronic HCV genotype 3 infection. Last November, FDA issued a complete response letter for Daklinza to treat HCV genotype 1b infection.

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

Product: Daklinza daclatasvir (BMS-790052)
Business: Infectious
Molecular target: HCV NS5A protein
Description: Selective HCV NS5A protein inhibitor
Indication: Treat recurrent chronic HCV genotype 1b infection following an orthotopic liver transplantation
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment and pharmacokinetics; SVR4, SVR24 and safety
Status: Interim Phase II data
Milestone: NA

Interim data from 35 patients with recurrent chronic HCV genotype 1b infection following an orthotopic liver transplantation in the 2-part, open-label, European Phase II SATURN (TMC435HPC3016) trial showed that once-daily 150 mg oral Olysio simeprevir and 60 mg oral Daklinza daclatasvir plus ribavirin led to HCV RNA levels of <25 IU/mL in 90.5% of patients at the end of treatment at week 24 in part 1 of the trial (n=21). In part 2, 92.9% of patients receiving the combination had HCV RNA levels of <25 IU/mL at week 4 (n=14). Part 1 of the trial enrolled patients with METAVIR scores of F1 or F2 and part 2 enrolled patients with METAVIR scores of F1-F4. Patients also received concomitant stable immunosuppressive therapy with cyclosporine A or tacrolimus. Data were presented at the European Association for the Study of the Liver meeting in Vienna.

Simeprevir, an HCV NS3/4A protease inhibitor, is marketed as Olysio in the U.S., as Sovriad in Japan and Russia and as Galexos in Canada to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. In the EU, Olysio is approved to treat HCV genotypes 1 and 4 infection in combination with peginterferon, ribavirin and/or Sovaldi sofosbuvir from Gilead Sciences Inc. (NASDAQ:GILD, Foster City, Calif.). The Janssen Research & Development LLC unit of Johnson & Johnson (NYSE:JNJ, New Brunswick, N.J.) has ex-Nordic rights to develop and commercialize Olysio from Medivir (SSE:MVIR B, Huddinge, Sweden). Daklinza is approved in the EU and Japan for HCV infection. In March, FDA accepted for review a resubmitted NDA for Daklinza in combination with Sovaldi to treat chronic HCV genotype 3 infection. Last November, FDA issued a complete response letter for Daklinza to treat HCV genotype 1b infection.

**Conatus Pharmaceuticals Inc.** (NASDAQ:CNAT), San Diego, Calif.

Product: Emricasan (PF-3491390, IDN-6556, PF-03491390)
Business: Hepatic
Molecular target: Caspases
Description: Pan-caspase protease inhibitor
Indication: Treat non-alcoholic fatty liver disease (NAFLD)
Endpoint: Change from baseline in alanine aminotransferase (ALT) levels at day 28; change in aspartate aminotransferase (AST) levels, cytokeratin 18 (CK18; KRT18) and cleaved CK18 and caspase-3 (CASP3; CPP32)/caspase-7 (CASP7; MCH3)
Status: Additional Phase II data
Milestone: NA

Additional data from a double-blind, U.S. Phase II trial in 38 patients with NAFLD, including patients with non-alcoholic steatohepatitis (NASH), showed that twice-daily 25 mg emricasan led to a median

absolute reduction in ALT levels from baseline to day 28, the primary endpoint, of 25.8 U/L vs. 9.4 U/L for placebo ($p<0.05$). On secondary endpoints, emricasan led to a median relative reduction in AST levels of 22% from baseline to day 28 vs. 10% for placebo. Data were presented at the European Association for the Study of the Liver meeting in Vienna. Conatus previously reported that emricasan met the primary endpoint vs. placebo (see BioCentury, March 30).

**Conatus Pharmaceuticals Inc.** (NASDAQ:CNAT), San Diego, Calif.

Product: Emricasan (PF-3491390, IDN-6556, PF-03491390)
Business: Hepatic
Molecular target: Caspases
Description: Pan-caspase protease inhibitor
Indication: Treat acute-on-chronic liver failure (ACLF)
Endpoint: Pharmacokinetics; safety and clinical outcomes, including transplantation, progression to next organ failure and death
Status: Additional Phase II data
Milestone: NA

An *ad hoc* analysis of a double-blind, U.S. and U.K. Phase II trial in 21 patients with ACLF showed that twice-daily 5, 25 and 50 mg oral emricasan for 28 days produced 9 responders (n=17) vs. 2 for placebo (n=4). A patient was considered a responder if they met any of the following criteria: survival to day 28 or last known follow-up; improvement of ≥2 points from baseline in Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score; improvement of ≥5 points from baseline in Model for End-Stage Liver Disease (MELD) score; or an improvement of about 50% from baseline in total bilirubin levels. Data were presented at the European Association for the Study of the Liver meeting in Vienna. Conatus previously reported top-line data from the trial (see BioCentury, Feb. 16).

**Delenex Therapeutics AG**, Zurich, Switzerland

Product: DLX105 IV
Business: Inflammation
Molecular target: Tumor necrosis factor (TNF) alpha
Description: IV formulation of an anti-tumor necrosis factor (TNF) alpha mAb fragment
Indication: Treat Behcet's disease
Endpoint: NA
Status: Phase II data
Milestone: NA

A double-blind, placebo-controlled Phase II trial in 24 healthy volunteers showed that 3 doses levels of IV DLX105 produced "effective and fast tissue distribution." In a subsequent open-label trial in 6 patients with flaring Behcet's disease, a single dose of 10 mg/kg IV DLX105 led to rapid resolution of cutaneous and mucosal eruptions. Furthermore, the company said signs and symptoms of the preceding flare had almost completely disappeared within 1 week of injection. DLX105 was well tolerated.

**DelMar Pharmaceuticals Inc.** (OTCQX:DMPI), Vancouver, B.C.
**Guangxi Wuzhou Zhongheng Group Co. Ltd.** (Shanghai:600252), Wuzhou, China

Product: DAG for Injection (VAL-083)
Business: Cancer
Molecular target: DNA
Description: Small molecule bifunctional alkylating agent
Indication: Treat glioblastoma multiforme (GBM)
Endpoint: Maximum tolerated dose (MTD); objective response rate (ORR)
Status: Additional Phase I/II data
Milestone: NA

Data from 6 patients with refractory GBM in the 8th cohort of an open-label, U.S. Phase I/II trial showed that 50 mg/m$^2$ IV VAL-083 given on days 1-3 of a 21-day cycle led to dose-limiting toxicities (DLTs) of grade 3/4 thrombocytopenia, which resolved rapidly and spontaneously without concomitant treatment. Of the 37 patients enrolled in all 8 dose cohorts in the trial, 1.5-50 mg/m$^2$ VAL-083 led to 3 responses consisting of stable disease or a partial response. The trial is enrolling GBM patients previously treated with surgery and/or radiation if appropriate and who failed both Avastin bevacizumab and Temodar temozolomide unless contraindicated. Data were presented at the American Association for Cancer Research meeting in Philadelphia. DelMar previously reported data from the trial (see BioCentury, April 21, 2014; July 21, 2014 & Sept. 1, 2014). Guangxi Wuzhou's Guangxi Wuzhou Pharmaceutical Co. subsidiary has rights to VAL-083 in China, where it is known as DAG for Injection, to treat chronic myelogenous leukemia (CML) and lung cancer — its approved indications in China (see BioCentury, Nov. 5, 2012).

**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 (3Q15)

The double-blind, international Phase IIb DARWIN 2 trial in 283 patients with moderate to severe RA who had an inadequate response to methotrexate showed that once-daily 50, 100 and 200 mg filgotinib as monotherapy each met the primary endpoint of improving ACR20 response rate at week 12 vs. placebo (67%, 66% and 73%, respectively, vs. 31%, $p<0.001$ for all). Low-, mid- and high-dose filgotinib also met the secondary endpoints of improving ACR50 response rate at week 12 (36%, 34% and 44%, respectively,

vs. 11%, p<0.01 for all) and of reducing mean DAS28 score from baseline to week 12 (1.7, 2 and 2.3 points, respectively, vs. 1 point, p<0.001 for all) vs. placebo. Additionally, mid-dose filgotinib met the secondary endpoint of improving ACR70 response rate at week 12 vs. placebo (19% vs. 4%, p<0.05). Low- and high-dose filgotinib missed the ACR70 endpoint. Filgotinib was well tolerated.

Galapagos expects to report 24-week data from the trial in 3Q15. Last month, the company reported data from the Phase IIb DARWIN 1 trial of filgotinib as an add-on to methotrexate (see BioCentury, April 20). AbbVie and Galapagos are partnered to develop and commercialize filgotinib (see BioCentury, March 5, 2012 & May 27, 2013).

**Genmab A/S** (CSE:GEN; OTCBB:GMXAY), Copenhagen, Denmark
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland

Product: Arzerra ofatumumab (HuMax-CD20)
Business: Cancer
Molecular target: CD20
Description: Human mAb against CD20
Indication: Treat relapsed chronic lymphocytic leukemia (CLL)
Endpoint: Progression-free survival (PFS); overall survival (OS), overall response rate (ORR), time to progression, duration of response, safety, pharmacokinetics and quality of life (QOL)
Status: Phase III data
Milestone: NA

Top-line data from the open-label, international Phase III COMPLEMENT 2 trial in 365 patients with relapsed CLL showed that IV Arzerra plus fludarabine and cyclophosphamide met the primary endpoint of improving PFS vs. fludarabine and cyclophosphamide alone (p=0.0036). Arzerra is approved in the U.S. and EU to treat CLL refractory to fludarabine and alemtuzumab and as first-line treatment of CLL. Novartis has worldwide co-development and commercialization rights to Arzerra for cancer indications from Genmab (see BioCentury, April 28, 2014; Dec. 8, 2014 & March 23, 2015).

**Gilead Sciences Inc.** (NASDAQ:GILD), Foster City, Calif.

Product: Sovaldi sofosbuvir (GS-7977) (formerly PSI-7977)
Business: Infectious
Molecular target: HCV NS5B polymerase
Description: Nucleotide analog HCV NS5B polymerase inhibitor
Indication: Treat non-cirrhotic patients with chronic HCV genotype 1 infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment and safety
Status: Phase III data
Milestone: NA

The open-label, North American Phase III OPTIMIST-1 (TMC435HPC3017) trial in 310 non-cirrhotic, treatment-naive or treatment-experienced patients with chronic HCV genotype 1 infection showed that once-daily 150 mg Olysio simeprevir and 400 mg Sovaldi sofosbuvir led to an SVR 12 weeks after the end of treatment in 83% of patients who were treated for 8 weeks and in 97% of patients who were treated for 12 weeks vs. SVR12 rates of 83% and 87%, respectively, for historical controls. Historical controls consisted of patients previously treated with approved regimens containing a direct-acting antiviral, pegylated interferon and ribavirin. Data were presented at the European Association for the Study of the Liver meeting in Vienna.

Simeprevir, an HCV NS3/4A protease inhibitor, is marketed as Olysio in the U.S., as Sovriad in Japan and Russia and as Galexos in Canada to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. In the EU, Olysio is approved to treat HCV genotypes 1 and 4 infection in combination with peginterferon, ribavirin and/or Sovaldi. The Janssen Research & Development LLC unit of Johnson & Johnson (NYSE:JNJ, New Brunswick, N.J.) has ex-Nordic rights to develop and commercialize Olysio from Medivir (SSE:MVIR B, Huddinge, Sweden). Gilead markets Sovaldi in the U.S., EU and Canada to treat HCV infection.

**Gilead Sciences Inc.** (NASDAQ:GILD), Foster City, Calif.

Product: Sovaldi sofosbuvir (GS-7977) (formerly PSI-7977)
Business: Infectious
Molecular target: HCV NS5B polymerase
Description: Nucleotide analog HCV NS5B polymerase inhibitor
Indication: Treat cirrhotic patients with chronic HCV genotype 1 infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment and safety
Status: Phase III data
Milestone: NA

The open-label, North American Phase III OPTIMIST-2 (TMC435HPC3018) trial in 103 cirrhotic, treatment-naive or treatment-experienced patients with chronic HCV genotype 1 infection showed that once-daily 150 mg Olysio simeprevir and 400 mg Sovaldi sofosbuvir for 12 weeks led to an SVR 12 weeks after the end of treatment in 84% of patients vs. 70% for historical controls. Historical controls consisted of patients previously treated with approved regimens containing a direct-acting antiviral, pegylated interferon and ribavirin. Data were presented at the European Association for the Study of the Liver meeting in Vienna.

Simeprevir, an HCV NS3/4A protease inhibitor, is marketed as Olysio in the U.S., as Sovriad in Japan and Russia and as Galexos in Canada to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. In the EU, Olysio is approved to treat HCV genotypes 1 and 4 infection in combination with peginterferon, ribavirin and/or Sovaldi. The Janssen Research & Development LLC unit of Johnson & Johnson (NYSE:JNJ, New Brunswick, N.J.) has ex-Nordic rights to develop and commercialize Olysio from Medivir (SSE:MVIR

B, Huddinge, Sweden). Gilead markets Sovaldi in the U.S., EU and Canada to treat HCV infection.

**Gilead Sciences Inc.** (NASDAQ:GILD), Foster City, Calif.

Product: Sovaldi sofosbuvir (GS-7977) (formerly PSI-7977)
Business: Infectious
Molecular target: HCV NS5B polymerase
Description: Nucleotide analog HCV NS5B polymerase inhibitor
Indication: Treat HCV infection in cirrhotic patients and patients with post-liver transplant HCV recurrence
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment; HCV RNA levels and safety
Status: Phase III data
Milestone: NA

The open-label, U.S. Phase III ALLY-1 trial in 113 patients with HCV infection of any genotype and with advanced cirrhosis or post-liver transplant recurrence of HCV showed that once-daily 60 mg Daklinza daclatasvir and 400 mg Sovaldi sofosbuvir plus ribavirin for 12 weeks led to an SVR 12 weeks after the end of treatment, the primary endpoint, in 83% of patients with advanced cirrhosis (n=60) and in 94% of post-liver transplant patients with HCV recurrence (n=53) and. In patients with HCV genotype 1 infection, the SVR12 rate was 82% in patients with advanced cirrhosis and 95% in post-liver transplant patients with HCV recurrence. Additionally, 97% of post-liver transplant patients with HCV genotype 1a infection and 91% of post-liver transplant patients with HCV genotype 3 infection achieved an SVR12. Furthermore, 56% of patients with decompensated cirrhosis Child-Pugh class C (n=16) achieved an SVR12.

Four advanced cirrhotic patients received a liver transplant during treatment and all 4 achieved an SVR12. One patient discontinued treatment after 31 days due to headache but still achieved an SVR12. There were 9 relapses post-treatment in the cirrhosis cohort and 1 patient had detectable HCV RNA levels at the end of treatment. There were no on-treatment virologic breakthroughs. There were 3 relapses in the post-transplantation cohort. All 12 patients who relapsed are being treated with Daklinza and Sovaldi plus ribavirin for 24 weeks. Data were presented at the European Association for the Study of the Liver meeting in Vienna.

Gilead markets Sovaldi in the U.S., EU and Canada to treat HCV infection. Daklinza, a selective HCV NS5A protein inhibitor from Bristol-Myers Squibb Co. (NYSE:BMY, New York, N.Y.), is approved in the EU and Japan for HCV infection. In March, FDA accepted for review a resubmitted NDA for Daklinza in combination with Sovaldi to treat chronic HCV genotype 3 infection. Last November, FDA issued a complete response letter for Daklinza to treat HCV genotype 1b infection.

**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

Product: JNJ-56914845 (formerly GSK2336805, 2336805)
Business: Infectious
Molecular target: HCV NS5A protein
Description: HCV NS5A protein inhibitor
Indication: Treat chronic HCV genotype 1 infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment and safety; SVR4, SVR24, HCV RNA levels from baseline up to 24 weeks after the end of treatment and number of patients with on-treatment virologic failure, viral relapse and undetectable HCV RNA
Status: Phase IIa data
Milestone: NA

Medivir AB (SSE:MVIR B, Huddinge, Sweden) reported data from the open-label, European Phase IIa HPC2001 trial in patients with chronic HCV genotype 1 infection evaluating an all-oral regimen of once-daily Olysio simeprevir plus TMC647055 and low-dose ritonavir with or without 30 or 60 mg JNJ-56914845 for 12 weeks. In patients who received Olysio plus TMC647055 and low-dose ritonavir with ribavirin, up to 86% achieved an SVR12. In patients who received Olysio plus TMC647055 and low-dose ritonavir without ribavirin, up to 50% achieved an SVR12. In patients who received Olysio plus TMC647055 and low-dose ritonavir with 30 mg JNJ-56914845 (n=22), 82% achieved an SVR12. In patients who received Olysio plus TMC647055 and low-dose ritonavir with 60 mg JNJ-56914845 (n=22), 95% achieved an SVR12. Data were presented at the Asian Pacific Association for the Study of the Liver meeting in Istanbul.

Simeprevir, an HCV NS3/4A protease inhibitor, is marketed as Olysio in the U.S., as Sovriad in Japan and Russia and as Galexos in Canada to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. In the EU, Olysio is approved to treat HCV genotypes 1 and 4 infection in combination with peginterferon, ribavirin and/or Sovaldi sofosbuvir from Gilead Sciences Inc. (NASDAQ:GILD, Foster City, Calif.). J&J's Janssen Research & Development LLC unit has ex-Nordic rights to develop and commercialize Olysio from Medivir. J&J's TMC647055 is a non-nucleoside HCV NS5B polymerase inhibitor. J&J has rights to JNJ-56914845 from GlaxoSmithKline.

**Gradalis Inc.**, Dallas, Texas

Product: Vigil vaccine (formerly FANG vaccine)
Business: Cancer
Molecular target: Transforming growth factor (TGF) beta 1 (TGFB1); Transforming growth factor (TGF) beta 2 (TGFB2)
Description: Autologous tumor-based vaccine composed of a plasmid encoding GM-CSF and a bi-functional short hairpin RNA (shRNA) that downregulates TGFB1 and TGFB2
Indication: Treat stage IIIc or IV ovarian cancer

Endpoint: Time to recurrence; immune function
Status: Additional Phase II data
Milestone: NA

Additional data from an open-label, U.S. Phase II trial in 31 patients with stage IIIc or IV ovarian cancer showed that median relapse-free survival (RFS) was 19.3 months in patients receiving once-monthly intradermal Vigil vaccine for up to 12 months plus standard of care (SOC) vs. 12.4 months for SOC alone (p=0.84). Standard of care consisted of tumor removal and chemotherapy. Data were presented at the Society of Gynecologic Oncology meeting in Chicago. Gradalis previously reported interim data from 17 evaluable patients (see BioCentury, June 3, 2013).

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

Product: TMC647055
Business: Infectious
Molecular target: HCV NS5B polymerase
Description: Non-nucleoside HCV NS5B polymerase inhibitor
Indication: Treat chronic HCV genotype 1 infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment and safety; SVR4, SVR24, HCV RNA levels from baseline up to 24 weeks after the end of treatment and number of patients with on-treatment virologic failure, viral relapse and undetectable HCV RNA
Status: Phase IIa data
Milestone: NA

Medivir AB (SSE:MVIR B, Huddinge, Sweden) reported data from the open-label, European Phase IIa HPC2001 trial in patients with chronic HCV genotype 1 infection evaluating an all-oral regimen of once-daily Olysio simeprevir plus TMC647055 and low-dose ritonavir with or without 30 or 60 mg JNJ-56914845 for 12 weeks. In patients who received Olysio plus TMC647055 and low-dose ritonavir with ribavirin, up to 86% achieved an SVR12. In patients who received Olysio plus TMC647055 and low-dose ritonavir without ribavirin, up to 50% achieved an SVR12. In patients who received Olysio plus TMC647055 and low-dose ritonavir with 30 mg JNJ-56914845 (n=22), 82% achieved an SVR12. In patients who received Olysio plus TMC647055 and low-dose ritonavir with 60 mg JNJ-56914845 (n=22), 95% achieved an SVR12. Data were presented at the Asian Pacific Association for the Study of the Liver meeting in Istanbul.

Simeprevir, an HCV NS3/4A protease inhibitor, is marketed as Olysio in the U.S., as Sovriad in Japan and Russia and as Galexos in Canada to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. In the EU, Olysio is approved to treat HCV genotypes 1 and 4 infection in combination with peginterferon, ribavirin and/or Sovaldi sofosbuvir from Gilead Sciences Inc. (NASDAQ:GILD, Foster City, Calif.). J&J's Janssen Research & Development LLC unit has ex-Nordic rights to develop and commercialize Olysio from Medivir. J&J has rights to JNJ-56914845, an HCV NS5A protein inhibitor, from GlaxoSmithKline plc (LSE:GSK; NYSE:GSK, London, U.K.).

**MediciNova Inc.** (NASDAQ:MNOV; JASDAQ:4875), San Diego, Calif.
**Kyorin Pharmaceutical Co. Ltd.** (Tokyo:4569), Tokyo, Japan

Product: Ibudilast (MN-166, AV411)
Business: Neurology
Molecular target: Phosphodiesterase-4 (PDE-4); Macrophage migration inhibitory factor (MIF)
Description: Oral small molecule inhibitor of phosphodiesterase-4 (PDE-4), PDE-10 and macrophage migration inhibitory factor (MIF) that suppresses pro-inflammatory cytokines
Indication: Treat amyotrophic lateral sclerosis (ALS)
Endpoint: Safety; Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R), slow vital capacity (SVC), maximum inspiratory pressure (MIP), forced expiratory volume in 1 second (FEV1), muscle strength and non-invasive ventilation utilization
Status: Interim Phase II data
Milestone: NA

Interim data from 21 ALS patients in a double-blind, U.S. Phase II trial showed that once-daily 60 mg oral ibudilast plus riluzole led to no safety or tolerability concerns after 3 months of treatment compared to placebo plus riluzole. Based on the interim data, an independent safety monitor recommended that the trial continue as planned. The trial is evaluating ibudilast or placebo plus riluzole for 6 months followed by a 6-month, open-label extension. Data were presented at the American Academy of Neurology meeting in Washington, D.C. MediciNova licensed ibudilast from Kyorin.

**Medivir AB** (SSE:MVIR B), Huddinge, Sweden
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

Product: Olysio simeprevir (Sovriad, Galexos) (TMC435) (formerly TMC435350)
Business: Infectious
Molecular target: HCV NS3/4A protease complex
Description: HCV NS3/4A protease inhibitor
Indication: Treat chronic HCV genotype 1 infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment and safety; SVR4, SVR24, HCV RNA levels from baseline up to 24 weeks after the end of treatment and number of patients with on-treatment virologic failure, viral relapse and undetectable HCV RNA
Status: Phase IIa data
Milestone: NA

Medivir reported data from the open-label, European Phase IIa HPC2001 trial in patients with chronic HCV genotype 1 infection evaluating an all-oral regimen of once-daily Olysio simeprevir plus TMC647055 and low-dose ritonavir with or without 30 or 60 mg JNJ-56914845 for 12 weeks. In patients who received Olysio plus TMC647055 and low-dose ritonavir with ribavirin,

up to 86% achieved an SVR12. In patients who received Olysio plus TMC647055 and low-dose ritonavir without ribavirin, up to 50% achieved an SVR12. In patients who received Olysio plus TMC647055 and low-dose ritonavir with 30 mg JNJ-56914845 (n=22), 82% achieved an SVR12. In patients who received Olysio plus TMC647055 and low-dose ritonavir with 60 mg JNJ-56914845 (n=22), 95% achieved an SVR12. Data were presented at the Asian Pacific Association for the Study of the Liver meeting in Istanbul.

Simeprevir is marketed as Olysio in the U.S., as Sovriad in Japan and Russia and as Galexos in Canada to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. In the EU, Olysio is approved to treat HCV genotypes 1 and 4 infection in combination with peginterferon, ribavirin and/or Sovaldi sofosbuvir from Gilead Sciences Inc. (NASDAQ:GILD, Foster City, Calif.). J&J's Janssen Research & Development LLC unit has ex-Nordic rights to develop and commercialize Olysio from Medivir. J&J's TMC647055 is a non-nucleoside HCV NS5B polymerase inhibitor. J&J has rights to JNJ-56914845, an HCV NS5A protein inhibitor, from GlaxoSmithKline plc (LSE:GSK; NYSE:GSK, London, U.K.).

**Medivir AB** (SSE:MVIR B), Huddinge, Sweden
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

Product: Olysio simeprevir (Sovriad, Galexos) (TMC435) (formerly TMC435350)
Business: Infectious
Molecular target: HCV NS3/4A protease complex
Description: HCV NS3/4A protease inhibitor
Indication: Treat non-cirrhotic patients with chronic HCV genotype 1 infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment and safety
Status: Phase III data
Milestone: NA

The open-label, North American Phase III OPTIMIST-1 (TMC435HPC3017) trial in 310 non-cirrhotic, treatment-naive or treatment-experienced patients with chronic HCV genotype 1 infection showed that once-daily 150 mg Olysio simeprevir and 400 mg Sovaldi sofosbuvir led to an SVR 12 weeks after the end of treatment in 83% of patients who were treated for 8 weeks and in 97% of patients who were treated for 12 weeks vs. SVR12 rates of 83% and 87%, respectively, for historical controls. Historical controls consisted of patients previously treated with approved regimens containing a direct-acting antiviral, pegylated interferon and ribavirin. Data were presented at the European Association for the Study of the Liver meeting in Vienna.

Simeprevir is marketed as Olysio in the U.S., as Sovriad in Japan and Russia and as Galexos in Canada to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. In the EU, Olysio is approved to treat HCV genotypes 1 and 4 infection in combination with peginterferon, ribavirin and/or Sovaldi from Gilead Sciences Inc. (NASDAQ:GILD, Foster City, Calif.). J&J's Janssen Research & Development LLC unit has ex-Nordic rights to develop and commercialize Olysio from Medivir. Gilead markets Sovaldi, a nucleotide analog HCV NS5B polymerase inhibitor, in the U.S., EU and Canada to treat HCV infection.

**Medivir AB** (SSE:MVIR B), Huddinge, Sweden
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

Product: Olysio simeprevir (Sovriad, Galexos) (TMC435) (formerly TMC435350)
Business: Infectious
Molecular target: HCV NS3/4A protease complex
Description: HCV NS3/4A protease inhibitor
Indication: Treat cirrhotic patients with chronic HCV genotype 1 infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment and safety
Status: Phase III data
Milestone: NA

The open-label, North American Phase III OPTIMIST-2 (TMC435HPC3018) trial in 103 cirrhotic, treatment-naive or treatment-experienced patients with chronic HCV genotype 1 infection showed that once-daily 150 mg Olysio simeprevir and 400 mg Sovaldi sofosbuvir for 12 weeks led to an SVR 12 weeks after the end of treatment in 84% of patients vs. 70% for historical controls. Historical controls consisted of patients previously treated with approved regimens containing a direct-acting antiviral, pegylated interferon and ribavirin. Data were presented at the European Association for the Study of the Liver meeting in Vienna.

Simeprevir is marketed as Olysio in the U.S., as Sovriad in Japan and Russia and as Galexos in Canada to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. In the EU, Olysio is approved to treat HCV genotypes 1 and 4 infection in combination with peginterferon, ribavirin and/or Sovaldi from Gilead Sciences Inc. (NASDAQ:GILD, Foster City, Calif.). J&J's Janssen Research & Development LLC unit has ex-Nordic rights to develop and commercialize Olysio from Medivir. Gilead markets Sovaldi, a nucleotide analog HCV NS5B polymerase inhibitor, in the U.S., EU and Canada to treat HCV infection.

**Medivir AB** (SSE:MVIR B), Huddinge, Sweden
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

Product: Olysio simeprevir (Sovriad, Galexos) (TMC435) (formerly TMC435350)
Business: Infectious
Molecular target: HCV NS3/4A protease complex
Description: HCV NS3/4A protease inhibitor

Indication: Treat recurrent chronic HCV genotype 1b infection following an orthotopic liver transplantation
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment and pharmacokinetics; SVR4, SVR24 and safety
Status: Interim Phase II data
Milestone: NA

Interim data from 35 patients with recurrent chronic HCV genotype 1b infection following an orthotopic liver transplantation in the 2-part, open-label, European Phase II SATURN (TMC435HPC3016) trial showed that once-daily 150 mg oral Olysio simeprevir and 60 mg oral Daklinza daclatasvir plus ribavirin led to HCV RNA levels of <25 IU/mL in 90.5% of patients at the end of treatment at week 24 in part 1 of the trial (n=21). In part 2, 92.9% of patients receiving the combination had HCV RNA levels of <25 IU/mL at week 4 (n=14). Part 1 of the trial enrolled patients with METAVIR scores of F1 or F2 and part 2 enrolled patients with METAVIR scores of F1-F4. Patients also received concomitant stable immunosuppressive therapy with cyclosporine A or tacrolimus. Data were presented at the European Association for the Study of the Liver meeting in Vienna.

Simeprevir is marketed as Olysio in the U.S., as Sovriad in Japan and Russia and as Galexos in Canada to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. In the EU, Olysio is approved to treat HCV genotypes 1 and 4 infection in combination with peginterferon, ribavirin and/or Sovaldi sofosbuvir from Gilead Sciences Inc. (NASDAQ:GILD, Foster City, Calif.). J&J's Janssen Research & Development LLC unit has ex-Nordic rights to develop and commercialize Olysio from Medivir. Daklinza, a selective HCV NS5A protein inhibitor from Bristol-Myers Squibb Co. (NYSE:BMY, New York, N.Y.), is approved in the EU and Japan for HCV infection. In March, FDA accepted for review a resubmitted NDA for Daklinza in combination with Sovaldi to treat chronic HCV genotype 3 infection. Last November, FDA issued a complete response letter for Daklinza to treat HCV genotype 1b infection.

**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.

Product: Grazoprevir/elbasvir (MK-5172/MK-8742)
Business: Infectious
Molecular target: HCV NS3/4A protease complex; HCV NS5A protein
Description: Fixed-dose oral combination of grazoprevir, an HCV NS3/4A protease inhibitor, and elbasvir, an HCV NS5A protein inhibitor
Indication: Treat chronic HCV genotype 1 infection in patients with chronic kidney disease (CKD)
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment, safety and discontinuations due to adverse events; SVR4 and SVR24
Status: Phase II/III data
Milestone: Submit NDA (1H15)

The double-blind, placebo-controlled Phase II/III C-SURFER trial in 116 evaluable patients with chronic HCV genotype 1 infection and advanced CKD with or without liver cirrhosis showed that once-daily oral 100 mg grazoprevir/50 mg elbasvir for 12 weeks led to an SVR 12 weeks after the end of treatment in 99% of patients. Six patients were excluded from the pre-specified primary efficacy analysis due to missing data caused by death or early discontinuation for reasons unrelated to treatment. The trial included an immediate treatment group (ITG) in which patients received blinded grazoprevir/elbasvir for 12 weeks (n=111); a deferred treatment group (DTG) in which patients which received placebo for 12 weeks followed by a 4-week follow-up period and then treatment with open-label grazoprevir/elbasvir for 12 weeks (n=113); and an open-label arm in which patients received grazoprevir/elbasvir for 12 weeks for intensive pharmacokinetic sampling (n=11). There were no discontinuations due to adverse events in the ITG arm vs. 5 discontinuations in the DTG arm. The most common treatment-related adverse events reported were headache, nausea and fatigue. The trial enrolled treatment-naïve patients and patients who failed prior pegylated interferon HCV therapy. Data were presented at the European Association for the Study of the Liver meeting in Vienna.

**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.

Product: Grazoprevir/elbasvir (MK-5172/MK-8742)
Business: Infectious
Molecular target: HCV NS3/4A protease complex; HCV NS5A protein
Description: Fixed-dose oral combination of grazoprevir, an HCV NS3/4A protease inhibitor, and elbasvir, an HCV NS5A protein inhibitor
Indication: Treat chronic HCV genotype 1, 4 or 6 infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment, safety and discontinuations due to adverse events; SVR4 and SVR24
Status: Phase III data
Milestone: Submit NDA (1H15)

The double-blind, placebo-controlled Phase III C-EDGE TN trial in 316 evaluable treatment-naïve patients with or without cirrhosis with chronic HCV genotype 1, 4 or 6 infection showed that once-daily oral 100 mg grazoprevir/50 mg elbasvir for 12 weeks led to an SVR 12 weeks after the end of treatment in 95% of patients in the immediate treatment group (ITG). The trial also included a deferred treatment group (DTG) in which patients received placebo for 12 weeks followed by a 4-week follow-up period and then treatment with grazoprevir/elbasvir for 12 weeks. The SVR12 rate was 97% in cirrhotic patients (n=70); 94% in non-cirrhotic patients (n=246); 92% in patients with HCV genotype 1a infection (n=157); 99% in patients with HCV genotype 1b or other genotype 1 infection (n=131); 100% in patients with HCV genotype 4 infection (n=18); and 80% in patients with HCV genotype 6 infection (n=10). In the ITG,

there were 13 cases of virologic failure, including 1 case of virologic breakthrough and 12 virologic relapses. The most common adverse events reported were headache, fatigue, nausea and arthralgia. Data were presented at the European Association for the Study of the Liver meeting in Vienna and published in the *Annals of Internal Medicine*.

**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.

Product: Grazoprevir/elbasvir (MK-5172/MK-8742)
Business: Infectious
Molecular target: HCV NS3/4A protease complex; HCV NS5A protein
Description: Fixed-dose oral combination of grazoprevir, an HCV NS3/4A protease inhibitor, and elbasvir, an HCV NS5A protein inhibitor
Indication: Treat chronic HCV genotype 1, 4 or 6 and HIV co-infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment, safety and discontinuations due to adverse events; SVR24
Status: Phase III data
Milestone: Submit NDA (1H15)

The open-label Phase III C-EDGE COINFECTION trial in 218 evaluable treatment-naïve patients with or without cirrhosis with chronic HCV genotype 1, 4 or 6 and HIV co-infection showed that once-daily oral 100 mg grazoprevir/50 mg elbasvir for 12 weeks led to an SVR 12 weeks after the end of treatment in 95% of patients. The SVR12 rate was 100% in cirrhotic patients (n=35); 94% in non-cirrhotic patients (n=183); 94% in patients with HCV genotype 1a infection (n=144); 96% in patients with HCV genotype 1b or other genotype 1 infection (n=45); 96% in patients with HCV genotype 4 infection (n=28); and 100% in patients with HCV genotype 6 infection (n=1). There were 7 cases of virologic failure, including 6 virologic relapses and 1 reinfection. The most common adverse events reported were fatigue, headache and nausea. Data were presented at the European Association for the Study of the Liver meeting in Vienna.

**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.

Product: Grazoprevir/elbasvir (MK-5172/MK-8742)
Business: Infectious
Molecular target: HCV NS3/4A protease complex; HCV NS5A protein
Description: Fixed-dose oral combination of grazoprevir, an HCV NS3/4A protease inhibitor, and elbasvir, an HCV NS5A protein inhibitor
Indication: Treat chronic HCV genotype 1, 4 or 6 infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment, safety and discontinuations due to adverse events; SVR24
Status: Phase III data
Milestone: Submit NDA (1H15)

The open-label Phase III C-EDGE TE trial in 105 evaluable treatment-naïve patients with or without cirrhosis with chronic HCV genotype 1, 4 or 6 infection showed that once-daily oral 100 mg grazoprevir/50 mg elbasvir without ribavirin for 12 weeks led to an SVR 12 weeks after the end of treatment in 92% of patients. The SVR12 rate was 89% in cirrhotic patients (n=37); 94% in non-cirrhotic patients (n=68); 90% in patients with HCV genotype 1a infection (n=61); 100% in patients with HCV genotype 1b or other genotype 1 infection (n=35); and 78% in patients with HCV genotype 4 infection (n=9).

In 104 evaluable treatment-naïve patients with or without cirrhosis with chronic HCV genotype 1, 4 or 6 infection, grazoprevir/elbasvir plus ribavirin for 12 weeks led to an SVR12 rate of 94%. The SVR12 rate was 89% in cirrhotic patients (n=35); 97% in non-cirrhotic patients (n=69); 93% in patients with HCV genotype 1a infection (n=60); 97% in patients with HCV genotype 1b or other genotype 1 infection (n=29); and 93% in patients with HCV genotype 4 infection (n=15).

In 105 evaluable treatment-naïve patients with or without cirrhosis with chronic HCV genotype 1, 4 or 6 infection, grazoprevir/elbasvir without ribavirin for 16 weeks led to an SVR12 rate of 92%. The SVR12 rate was 92% in cirrhotic patients (n=38); 93% in non-cirrhotic patients (n=67); 94% in patients with HCV genotype 1a infection (n=48); 96% in patients with HCV genotype 1b or other genotype 1 infection (n=48); 60% in patients with HCV genotype 4 infection (n=5); and 75% in patients with HCV genotype 6 infection (n=4).

In 106 evaluable treatment-naïve patients with or without cirrhosis with chronic HCV genotype 1, 4 or 6 infection, grazoprevir/elbasvir plus ribavirin for 16 weeks led to an SVR12 rate of 97%. The SVR12 rate was 100% in cirrhotic patients (n=37); 96% in non-cirrhotic patients (n=69); 95% in patients with HCV genotype 1a infection (n=58); 100% in patients with HCV genotype 1b or other genotype 1 infection (n=38); 100% in patients with HCV genotype 4 infection (n=8); and 100% in patients with HCV genotype 6 infection (n=2). Data were presented at the European Association for the Study of the Liver meeting in Vienna.

**Merrimack Pharmaceuticals Inc.** (NASDAQ:MACK), Cambridge, Mass.

Product: MM-302
Business: Cancer
Molecular target: Epidermal growth factor receptor 2 (HER2) (EGFR2) (ErbB2) (neu)
Description: Pegylated liposomal doxorubicin formulation targeting HER2
Indication: Treat advanced HER2-positive breast cancer
Endpoint: Safety and maximum tolerated dose (MTD); dose-limiting toxicity (DLT), overall response rate (ORR), duration of response, progression-free survival (PFS) and pharmacokinetics

Status: Phase I final data
Milestone: NA

Final data from 62 patients with advanced HER2-positive breast cancer in an open-label, dose-escalation, U.S. Phase I trial showed that IV MM-302 at doses of ≥30 mg/m$^2$ every 4 weeks as monotherapy or in combination with Herceptin trastuzumab with and without cyclophosphamide led to a median PFS of 7.6 months and an ORR of 11%. In anthracycline-naïve patients (n=25), median PFS was 11 months and the ORR was 24%. Data were presented at the American Association for Cancer Research Meeting in Philadelphia. Merrimack has previously reported data from the trial (see BioCentury, Dec. 17, 2012 & Jan. 20, 2014). MM-302 is in the Phase II HERMIONE trial to treat anthracycline-naive patients with HER2-positive, locally advanced or metastatic breast cancer.

**Mitotech S.A.**, Luxembourg, Luxembourg

Product: SkQ1, Visomitin
Business: Ophthalmic
Molecular target: NA
Description: Small molecule designed to reduce oxidative stress inside mitochondria
Indication: Treat dry eye syndrome
Endpoint: Fluorescein staining and worst dry eye symptom; safety
Status: Phase II data
Milestone: Start Phase III (4Q15)

A double-blind, U.S. Phase II trial in 90 patients with moderate to severe dry syndrome showed that topical SkQ1 ophthalmic solution significantly improved central and total corneal fluorescein staining following challenge in a controlled adverse environment chamber vs. placebo (p=0.036 and p=0.045, respectively). SkQ1 was well tolerated with no unexpected or serious ocular events reported.

**Ono Pharmaceutical Co. Ltd.** (Tokyo:4528), Osaka, Japan
**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.

Product: Januvia sitagliptin (Tesavel, Glactiv)
Business: Endocrine/Metabolic
Molecular target: Dipeptidyl peptidase-4 (DPP-4) (CD26)
Description: Dipeptidyl peptidase-4 (DPP-4) inhibitor
Indication: Treat Type II diabetes
Endpoint: Time to first confirmed cardiovascular (CV) event, defined as a composite of CV-related death, non-fatal myocardial infarction (MI), non-fatal stroke or unstable angina requiring hospitalization; time to all-cause mortality and congestive heart failure (CHF) and change in renal function
Status: Phase III data
Milestone: NA

The double-blind, international Phase III TECOS CV safety trial in 14,724 Type II diabetics with a history of CV disease showed that once-daily oral Januvia met the primary endpoint of non-inferiority to placebo in the time to first confirmed CV event, defined as a composite of CV-related death, non-fatal MI, non-fatal stroke or unstable angina requiring hospitalization. On a secondary endpoint, there was no increase in hospitalization for heart failure in the Januvia arm compared to placebo. Data will be presented at the American Diabetes Association meeting in Boston in June. Ono has a license to co-develop the product in Japan under a 2004 deal with Merck, which markets Januvia as an adjunct to diet and exercise to improve glycemic control in adults with Type II diabetes (see BioCentury, Nov. 15, 2004).

**Otonomy Inc.** (NASDAQ:OTIC), San Diego, Calif.

Product: AuriPro (formerly OTO-201)
Business: Infectious
Molecular target: DNA gyrase
Description: Sustained-release gel formulation of ciprofloxacin
Indication: Intraoperative treatment of middle ear effusion in pediatric patients requiring tympanostomy tube placement surgery
Endpoint: Cumulative proportion of study treatment failures through day 15, defined as the presence of otorrhea or use of antibiotic rescue medication; safety and microbiological response
Status: Additional Phase III data
Milestone: Market launch (1Q16)

Additional data from a pair of identical, double-blind, North American Phase III trials in a total of 532 patients ages 6 months to 17 years old with bilateral middle ear effusion requiring tympanostomy tube placement surgery showed that a single intratympanic injection of AuriPro reduced the risk of treatment failure through day 15, the primary endpoint — defined as the occurrence of post-operative otorrhea or any use of rescue antibiotics — by 49% vs. sham control (p<0.001). AuriPro also reduced the rate of post-operative otorrhea or use of rescue antibiotics for documented otorrhea or otitis media by 62% vs. sham control (p≤0.004). Data were presented at the American Society of Pediatric Otolaryngology meeting in Boston. Otonomy previously reported that AuriPro met the primary endpoint in both trials vs. sham control (see BioCentury, July 14, 2014). On April 28, FDA accepted for review an NDA for AuriPro to treat middle ear effusion in pediatric patients undergoing tympanostomy tube placement surgery. The PDUFA date is expected to be in late December.

**Tracon Pharmaceuticals Inc.** (NASDAQ:TCON), San Diego, Calif.

Product: Methoxyamine (TRC102)
Business: Cancer
Molecular target: Not applicable
Description: Small molecule inhibitor of the DNA base-excision repair pathway that reverses chemotherapy resistance
Indication: Treat relapsed solid tumors
Endpoint: Safety and maximum tolerated dose (MTD); pharmacokinetics
Status: Phase I data
Milestone: NA

An open-label, dose-escalation, U.S. Phase I trial in 27 patients with relapsed solid tumors showed that once-daily oral TRC102 plus temozolomide for the first 5 days of a 28-day cycle led to 2 partial responses and 3 cases of stable disease. The combination of TRC102 and temozolomide was well tolerated up to dose levels of 100 mg and 150 mg/m$^2$, respectively. The MTD has not yet been reached. Data were presented at the American Association for Cancer Research meeting in Philadelphia.

**Viralytics Ltd.** (ASX:VLA; OTCQX:VRACY), Pymble, Australia

Product: Cavatak
Business: Cancer
Molecular target: Intercellular adhesion molecule-1 (ICAM-1) (CD54)
Description: Coxsackievirus A21 (CVA21)
Indication: Treat solid tumors
Endpoint: Tracking to malignant tumors (part 1), safety, objective response rate (ORR) and Phase II dose (part 2)
Status: Interim Phase I/II data
Milestone: NA

Interim data from 6 patients with advanced cancer in the open-label, dose-escalation, U.K. Phase I/II STORM trial showed that multiple doses of IV Cavatak were generally well tolerated with no treatment-related grade 2, 3 or 4 adverse events reported. Viralytics also said 4 patients have exhibited signs of tumor-specific secondary viral replication and that escalating viral dose has been associated with increased antitumor activity on some individual lesions. Data were presented at the American Association for Cancer Research meeting in Philadelphia.

**Viralytics Ltd.** (ASX:VLA; OTCQX:VRACY), Pymble, Australia

Product: Cavatak
Business: Cancer
Molecular target: Intercellular adhesion molecule-1 (ICAM-1) (CD54)
Description: Coxsackievirus A21 (CVA21)
Indication: Treat stage IIIc/IV metastatic melanoma
Endpoint: Immune-related progression-free survival (irPFS) at 6 months; objective response rate (ORR), PFS, 1-year survival, overall survival (OS) and quality of life (QOL)
Status: Updated Phase II data
Milestone: NA

Updated data from 57 evaluable patients with stage IIIc/IV malignant melanoma in the 2-stage, open-label, U.S. Phase II CALM trial showed that intratumoral Cavatak led to irPFS, the primary endpoint, in 22 patients at 6 months. Median irPFS was 4.2 months. Additionally, Cavatak led to an ORR of 28.1% and an interim 1-year OS rate of 75%. Data were presented at the American Association for Cancer Research meeting in Philadelphia. The company previously reported that Cavatak met the primary endpoint of ≥10 of 54 evaluable patients achieving irPFS at 6 months (see BioCentury, July 29, 2013; Sept. 30, 2013 & July 14, 2014). Final data will be presented at the American Society of Clinical Oncology meeting in Chicago on June 1.

CLINICAL NEWS

## CLINICAL STATUS

**Acacia Pharma Ltd.**, Cambridge, U.K.

Product: APD421 (formerly ACA1421)
Business: Gastrointestinal
Molecular target: Dopamine D2 receptor; Dopamine D3 receptor (DRD3)
Description: IV formulation of amisulpride, an off-patent dopamine D2 and D3 receptor antagonist
Indication: Prevent postoperative nausea and vomiting (PONV)
Endpoint: Complete response, defined as no vomiting or retching and no requirement for anti-emetic rescue medication in the first 24 hours after surgery; incidence and severity of nausea
Status: Phase III started
Milestone: NA

Acacia began a double-blind, placebo-controlled, international Phase III trial to evaluate a single dose of IV APD421 plus standard anti-emetic treatment in up to 1,200 high-risk patients ages ≥18 undergoing elective surgery under general anesthesia.

**Active Biotech AB** (SSE:ACTI), Lund, Sweden
**Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA), Petah Tikva, Israel

Product: Laquinimod (SAIK-MS)
Business: Autoimmune
Molecular target: S100 calcium binding protein A9 (S100A9) (calgranulin B) (MRP14)
Description: Oral quinoline-3-carboxamide immunomodulator
Indication: Treat primary progressive multiple sclerosis (PPMS)
Endpoint: Percent brain volume change (PBVC) as measured by MRI from baseline to week 48; time to confirmed disability progression, number of new T2 lesions and change in Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) score
Status: Phase II started
Milestone: Complete Phase II (2H17)

Teva began the double-blind, placebo-controlled, international Phase II ARPEGGIO trial to evaluate 0.6 and 1.5 mg oral laquinimod once daily in about 375 patients. Teva has exclusive, worldwide rights to laquinimod from Active Biotech (see BioCentury, Feb. 15, 2010).

**Cardio3 BioSciences S.A.** (Euronext:CARD), Mont-Saint-Guibert, Belgium

Product: CAR-NKG2D (CM-CS1)
Business: Cancer

Molecular target: Killer cell lectin-like receptor subfamily K member 1 (KLRK1) (CD314) (NKG2D)
Description: Autologous chimeric antigen receptor (CAR) T cells targeting killer cell lectin-like receptor subfamily K member 1 (KLRK1; CD314; NKG2D)
Indication: Treat hematologic malignancies
Endpoint: Safety and feasibility; progression-free survival (PFS) and function of CAR-NKG2D T cells
Status: Phase I started
Milestone: Complete Phase I (mid-2016)

Cardio3 began an open-label, U.S. Phase I trial to evaluate single doses of IV CAR-NKG2D in about 24 patients with acute myelogenous leukemia (AML) or multiple myeloma (MM). Patients will receive doses comprising 1x106, 3x106, 1x107 and 3x107 CAR-NKG2D T cells.

**Celldex Therapeutics Inc.** (NASDAQ:CLDX), Needham, Mass.

Product: Varlilumab (CDX-1127)
Business: Cancer
Molecular target: CD27
Description: Human mAb targeting CD27
Indication: Treat stage III or IV metastatic melanoma
Endpoint: Objective response rate (ORR); safety, immunogenicity, pharmacokinetics and antitumor activity
Status: Phase I/II started
Milestone: NA

Celldex began an open-label, U.S. Phase I/II trial to evaluate IV varlilumab and its subcutaneous CDX-1401 in combination with Yervoy ipilimumab and the adjuvant poly-ICLC in about 100 patients. The Phase I portion will test 0.3 and 3 mg/kg varlilumab plus Yervoy every 3 weeks for up to 4 cycles. The Phase II portion will test the recommended dose of varlilumab in combination with Yervoy in up to 48 patients whose tumors do not express cancer/testis antigen 1B (CTAG1B; NY-ESO-1) and in combination with Yervoy, CDX-1401 and poly-ICLC in up to 24 patients whose tumors express NY-ESO-1. CDX-1401 is a fusion protein consisting of a human mAb with specificity for the dendritic cell receptor linked to NY-ESO-1.

**Celldex Therapeutics Inc.** (NASDAQ:CLDX), Needham, Mass.

Product: CDX-1401
Business: Cancer
Molecular target: Cancer/testis antigen 1B (CTAG1B) (NY-ESO-1)
Description: Fusion protein consisting of a human mAb with specificity for the dendritic cell receptor linked to cancer/testis antigen 1B (CTAG1B; NY-ESO-1)
Indication: Treat stage III or IV metastatic melanoma
Endpoint: Objective response rate (ORR); safety, immunogenicity, pharmacokinetics and antitumor activity
Status: Phase I/II started
Milestone: NA

Celldex began an open-label, U.S. Phase I/II trial to evaluate its IV varlilumab (CDX-1127) and subcutaneous CDX-1401 in combination with Yervoy ipilimumab and the adjuvant poly-ICLC in about 100 patients. The Phase I portion will test 0.3 and 3 mg/kg varlilumab plus Yervoy every 3 weeks for up to 4 cycles. The Phase II portion will test the recommended dose of varlilumab in combination with Yervoy in up to 48 patients whose tumors do not express NY-ESO-1 and in combination with Yervoy, CDX-1401 and poly-ICLC in up to 24 patients whose tumors express NY-ESO-1. Varlilumab is a human mAb targeting CD27.

**ChemoCentryx Inc.** (NASDAQ:CCXI), Mountain View, Calif.

Product: CCX872
Business: Cancer
Molecular target: CC chemokine receptor 2 (CCR2) (CD192)
Description: Next-generation oral CC chemokine receptor 2 (CCR2; CD192) antagonist
Indication: Treat non-resectable pancreatic cancer
Endpoint: Progression-free survival (PFS) and grade 3 or 4 adverse events
Status: Phase Ib started
Milestone: Phase Ib preliminary data (year end 2015)

ChemoCentryx began an open-label Phase Ib trial to evaluate 150 mg oral CCX872 twice daily plus FOLFIRINOX chemotherapy for ≥12 weeks in up to 54 patients.

**Effimune S.A.S.**, Nantes, France

Product: FR104
Business: Autoimmune
Molecular target: CD28 receptor
Description: Pegylated monovalent antibody fragment antagonist of CD28 receptor
Indication: Treat immune-mediated disorders
Endpoint: Safety, pharmacokinetics and immunogenicity
Status: Phase I start
Milestone: Start Phase I (05/2015); Phase I data (early 2016)

This month, Effimune will begin a double-blind, placebo-controlled, Belgian Phase I trial to evaluate single and multiple ascending doses of IV FR104 in 70 healthy volunteers. The Janssen Biotech Inc. subsidiary of Johnson & Johnson (NYSE:JNJ, New Brunswick, N.J.) has an exclusive, worldwide option to FR104 (see BioCentury, Oct. 7, 2013).

**Galena Biopharma Inc.** (NASDAQ:GALE), Portland, Ore.
**Dr. Reddy's Laboratories Ltd.** (NYSE:RDY), Hyderabad, India

Product: NeuVax nelipepimut-S (E75)
Business: Cancer
Molecular target: NA

Description: Vaccine consisting of an immunogenic peptide derived from epidermal growth factor receptor 2 (EGFR2; HER2; ErbB2; neu) and sargramostim
Indication: Prevent recurrence of early stage, node-positive breast cancer
Endpoint: Disease-free survival (DFS) at 3 years; DFS at 5 and 10 years, overall survival (OS) at 3, 5 and 10 years, time to recurrence (TTR), time to local recurrence (TTLR), time to distant recurrence (TTDR), time to bone metastases (TTBM) and safety
Status: Completed Phase III enrollment
Milestone: NA

Galena completed enrollment of 758 patients in the double-blind, international Phase III PRESENT trial comparing intradermal NeuVax plus intradermal Leukine sargramostim vs. Leukine alone. Patients will receive NeuVax and Leukine monthly for 6 months followed by every 6 months for 30 months. The trial has an SPA from FDA. Dr. Reddy's has exclusive rights to develop and commercialize NeuVax in India (see BioCentury, Jan. 20, 2014).

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

Product: Cannabidiol (Epidiolex)
Business: Neurology
Molecular target: Cannabinoid receptors
Description: Oral liquid formulation of cannabidiol, a phytocannabinoid found in Cannabis sativa
Indication: Treat Dravet syndrome
Endpoint: Percentage change from baseline in convulsive seizure frequency during the maintenance period
Status: Phase III started
Milestone: Complete Phase III enrollment (2015); Phase II/III data (year end 2015); Phase III data (1Q16); submit NDA (mid-2016)

GW began a double-blind, placebo-controlled Phase III trial to evaluate 10 and 20 mg/kg oral Epidiolex twice daily for 14 weeks in 150 patients. The trial includes a long-term open-label extension study.

**Isarna Therapeutics GmbH**, Munich, Germany

Product: ISTH0036
Business: Ophthalmic
Molecular target: Transforming growth factor (TGF) beta 2 (TGFB2)
Description: Antisense oligonucleotide targeting transforming growth factor (TGF) beta 2 (TGFB2)
Indication: Treat open-angle glaucoma
Endpoint: Safety; change in intraocular pressure (IOP), number of interventions post-trabeculectomy and change in visual field from baseline to 1 year
Status: Phase I started
Milestone: NA

Isarna began an open-label, dose-escalation, German Phase I trial to evaluate intravitreal ISTH0036 in about 24-30 patients undergoing trabeculectomy. Patients will receive a single dose of ISTH0036 or ISTH0036 every other month.

**Isofol Medical AB**, Gothenburg, Sweden
**Merck KGaA** (Xetra:MRK), Darmstadt, Germany

Product: 6R-methylenetetrahydrofolate (Modufolin) (ISO-901)
Business: Other
Molecular target: NA
Description: Endogenous folate-based biomodulator
Indication: Mitigate high-dose methotrexate-induced toxicity
Endpoint: Frequency and severity grade of toxicity; number of high-dose methotrexate courses with rescue therapy classified as having met criteria for successful advancement
Status: Phase I/II started
Milestone: NA

Isofol began an open-label, European Phase I/II trial to evaluate 7.5, 15 and 30 mg/m$^2$ Modufolin in about 6 patients with osteosarcoma receiving treatment with methotrexate. Isofol has exclusive, worldwide rights to Modufolin from Merck (see BioCentury, Nov. 23, 2009).

**Merck KGaA** (Xetra:MRK), Darmstadt, Germany
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.

Product: Avelumab (MSB0010718C)
Business: Cancer
Molecular target: Programmed cell death 1 ligand 1 (PD-L1) (B7-H1) (CD274)
Description: Human IgG1 mAb against programmed cell death 1 ligand 1 (PD-L1; B7-H1; CD274)
Indication: Treat stage IIIB/IV non-small cell lung cancer (NSCLC)
Endpoint: Overall survival (OS) in PD-L1-positive patients; OS in all patients, progression-free survival (PFS), overall response rate (ORR) and patient-reported outcomes
Status: Phase III started
Milestone: NA

Merck and Pfizer began the open-label, international Phase III JAVELIN Lung 200 trial to compare 10 mg/kg IV avelumab every 2 weeks vs. 75 mg/m$^2$ IV docetaxel every 3 weeks in about 650 patients whose disease has progressed after a platinum-containing doublet. Pfizer and Merck are co-developing and co-commercializing Merck's avelumab as a single agent and in combination with other pipeline candidates (see BioCentury, Nov. 24, 2014).

**MorphoSys AG** (Xetra:MOR; Pink:MPSYF), Martinsried, Germany
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

Product: Guselkumab (CNTO 1959)
Business: Autoimmune
Molecular target: Interleukin-23 (IL-23)
Description: Human HuCAL mAb targeting the p19 subunit of IL-23

Indication: Treat psoriatic arthritis
Endpoint: Proportion of patients achieving a 20% improvement in the American College of Rheumatology criteria (ACR20) at week 24; change in Health Assessment Question-Disability Index (HAQ-DI) score, ACR20 at week 16, ACR50 at week 24 and Psoriasis Area and Severity Index (PASI) 75 response at week 24
Status: Phase II started
Milestone: NA

MorphoSys said Johnson & Johnson's Janssen Biotech Inc. unit began a double-blind, placebo-controlled, international Phase II trial to evaluate 100 mg subcutaneous guselkumab given at weeks 0, 4, 12, 20, 28, 36 and 44 in about 150 patients. Patients that qualify for early escape at week 16 will switch to open-label Stelara ustekinumab. At week 24, patients remaining in the placebo arm will receive guselkumab at weeks 24, 28, 36 and 44.

The start triggered an undisclosed milestone payment to MorphoSys under a 2000 deal in which the biotech used its HuCAL human combinatorial antibody library to generate antibodies for a range of indications and perform target discovery for Janssen. The discovery portion of the deal expired in late 2007 and MorphoSys is eligible for milestone payments and royalties (see BioCentury, Jan. 8, 2001).

**NeuroVive Pharmaceutical AB** (SSE:NVP), Lund, Sweden

Product: NeuroStat
Business: Inflammation
Molecular target: NA
Description: Cyclosporine A lipid emulsion formulated without Cremophor EL, a stabilizing solution
Indication: Treat severe traumatic brain injury (TBI)
Endpoint: Safety and pharmacokinetics
Status: Phase IIa ongoing
Milestone: NA

An independent safety committee recommended continuation to the 10 mg/kg dose of NeuroStat in the open-label, Danish Phase IIa CHIC trial based on interim data from 10 patients treated with the 5 mg/kg dose. The analysis included evaluation of blood concentrations of cyclosporin A, changes in intracranial pressure and blood samples collected to analyze possible organ injury. The trial is enrolling 20 patients with severe TBI to receive 5 or 10 mg/kg NeuroStat.

**Nimbus Therapeutics LLC**, Cambridge, Mass.

Product: NDI-010976
Business: Hepatic
Molecular target: Acetyl-Coenzyme A carboxylase (ACAC) (ACC)
Description: Allosteric acetyl-coenzyme A carboxylase (ACAC; ACC) inhibitor
Indication: Treat non-alcoholic steatohepatitis (NASH) and fatty liver disease-spectrum disorders
Endpoint: Safety, pharmacokinetics and maximum tolerated dose (MTD)
Status: Phase I started
Milestone: Complete Phase I (2015); start Phase II (early 2016)

Nimbus began an open-label Phase I trial to evaluate once- and twice-daily oral NDI-010976 in healthy volunteers. A subsequent Phase Ib trial will enroll obese patients with metabolic syndrome.

**Nuvo Research Inc.** (TSX:NRI), Mississauga, Ontario

Product: WF10 (formerly OXO-K993)
Business: Inflammation
Molecular target: Not available
Description: Tetrachlorodecaoxygen chlorite matrix
Indication: Treat allergic rhinitis
Endpoint: Patient symptoms and safety
Status: Phase II start
Milestone: Start Phase II (05/2015); Phase II data (year end 2015–early 2016)

This month, Nuvo will begin the double-blind, placebo-controlled, Canadian Phase II 2015 WF10 Trial to evaluate 0.5 mL/kg IV WF10 once daily for 5 days in about 146 patients with moderate to severe allergy to grass and ragweed pollen. Patients' symptoms will be recorded before the start of the grass allergy season in an environmental exposure chamber (EEC), in the field during the grass and ragweed allergy seasons and then in the EEC after the end of the ragweed season.

**OncoMed Pharmaceuticals Inc.** (NASDAQ:OMED), Redwood City, Calif.

Product: Demcizumab (OMP-21M18)
Business: Cancer
Molecular target: Delta-like 4 (DLL4)
Description: Humanized IgG2 mAb against delta-like 4 (DLL4)
Indication: First-line treatment of metastatic pancreatic cancer
Endpoint: Progression-free survival (PFS); overall survival (OS), overall response rate (ORR), duration of response, safety, immunogenicity and pharmacokinetics
Status: Phase II started
Milestone: NA

OncoMed began the 3-arm, double-blind, international Phase II YOSEMITE trial to evaluate 3.5 mg/kg IV demcizumab every 2 weeks for 70 days plus standard of care (SOC: Abraxane nab-paclitaxel and gemcitabine) in about 200 patients. The 3 arms consist of SOC plus placebo; SOC plus 1 course of demcizumab; and SOC plus 2 courses demcizumab separated by a 100-day washout period. Celgene Corp. (NASDAQ:CELG, Summit, N.J.) has exclusive options from OncoMed to jointly develop and commercialize up to 6 of OncoMed's cancer stem cell products, including demcizumab (see BioCentury, Dec. 9, 2013).

**Pharmaleads S.A.S.**, Paris, France

Product: PL37 (formerly Debio 0827)
Business: Neurology
Molecular target: Neutral endopeptidase (neprilysin) (MME) (NEP) (CD10); Alanyl membrane aminopeptidase (ANPEP) (APN) (CD13)
Description: Dual inhibitor of neutral endopeptidase (neprilysin; MME; NEP; CD10) and alanyl membrane aminopeptidase (ANPEP; APN; CD13)
Indication: Treat diabetic peripheral neuropathy (DPN)
Endpoint: Reduction of pain intensity; safety
Status: Phase IIa started
Milestone: Phase IIa data (year end 2015–early 2016)

Pharmaleads began a double-blind, placebo-controlled, European Phase IIa trial to evaluate 200 mg oral PL37 thrice daily plus pregabalin or gabapentin for 4 weeks in 108 patients previously treated with pregabalin or gabapentin.

**RepliCel Life Sciences Inc.** (OTCQB:REPCF; TSX-V:RP), Vancouver, B.C.

Product: RepliCel Tendon-01 (RCT-01)
Business: Musculoskeletal
Molecular target: NA
Description: Fibroblasts isolated from non-bulbar dermal sheath (NBDS) cells from a patient's healthy hair follicles that are replicated using RepliCel technology
Indication: Treat Achilles tendinosis
Endpoint: Safety; Victorian Institute of Sport Assessment-Achilles (VISA-A) questionnaire, pain on palpation and pain on loading, modified Tegner activity scale, quality of life (QOL) questionnaire and tendon condition
Status: Phase I/II started
Milestone: Phase I/II data (1H16)

RepliCel began the double-blind, placebo-controlled, Canadian Phase I/II ReaCT trial to evaluate ultrasound-guided injections of RCT-01 in 28 patients with unilateral, chronic Achilles tendinosis.

**Sihuan Pharmaceutical Holdings Group Ltd.** (HKSE:0460), Haikou, China

Product: Pirotinib (KBP5209, KBP-5209)
Business: Cancer
Molecular target: Epidermal growth factor receptor (EGFR)
Description: Second-generation, irreversible pan-EGFR tyrosine kinase inhibitor
Indication: Treat advanced solid tumors
Endpoint: Safety and pharmacokinetics; antitumor activity according to RECIST v1.1 criteria
Status: Phase I started
Milestone: NA

Sihuan began a dose-escalation, U.S. Phase I trial to evaluate oral pirotinib as a single agent in about 30 patients with advanced solid tumors, including non-small cell lung cancer (NSCLC), gastric and colorectal cancers.

**Strathspey Crown Holdings LLC**, Newport Beach, Calif.

Product: Evosyal, Evolus (DWP-450)
Business: Dermatology
Molecular target: NA
Description: Clostridium botulinum toxin type A neuromodulator
Indication: Treat glabellar lines (frown lines between the eyebrows)
Endpoint: Reduction of glabellar lines as assessed by investigator and subject at day 30; reduction of glabellar lines at max frown and at rest at day 120 and safety
Status: Completed Phase III enrollment
Milestone: NA

Strathspey's Alphaeon subsidiary completed enrollment in a pair of double-blind, placebo-controlled, U.S. Phase III trials evaluating injections of Evolus. The trials were each targeting 324 patients. Alphaeon gained exclusive rights to market Evolus in the U.S. and other international markets through Strathspey's 2013 acquisition of Evolus Inc. (see BioCentury, Oct. 14, 2013).

**VolitionRx Ltd.** (NYSE-M:VNRX), Singapore

Product: NuQ tests
Business: Diagnostic
Molecular target: NA
Description: Family of non-invasive blood tests for nucleosomes
Indication: Detect precancerous colorectal polyps
Endpoint: NA
Status: Clinical trial started
Milestone: NA

VolitionRx began a Danish clinical trial to evaluate up to 30 NuQ tests using blood samples from 300 patients with single or multiple precancerous polyps, 100 patients with early stage colorectal cancer and 400 subjects without polyps or colorectal cancers. The NuQ tests utilize the company's Nucleosomics platform, which identifies and measures circulating nucleosome structures in blood.

*Week ended 5/1/15. Shares after offering refers to shares outstanding. Proceeds are gross, not net. Shares offered don't include overallotments. Currency rates used in the week: A$=$0.7814; €=$1.0855; SEK=$0.1159*

FINANCIAL NEWS

## COMPLETED OFFERINGS

**Advaxis Inc.** (NASDAQ:ADXS), Princeton, N.J.
Business: Cancer
Date completed: 2015-04-30
Type: Follow-on
Raised: $53.2 million
Shares: 2.8 million
Price: $19
Shares after offering: 30 million
Underwriters: Jefferies; Barclays Capital; Guggenheim Securities; Janney Montgomery Scott; Aegis Capital; H.C. Wainwright
Overallotment: 420,000

**Amarantus BioScience Holdings Inc.** (OTCQB:AMBS), San Francisco, Calif.
Business: Neurology, Cardiovascular
Date completed: 2015-04-24
Type: Private placement of convertible preferred stock
Raised: $5 million
Shares: 1,087
Shares outstanding prior: 1 billion
Investor: Discover Growth Fund

Note: The series G stock bears an 8.25% dividend and converts at $0.06. The stock automatically converts after six years.

**Blueprint Medicines Corp.** (NASDAQ:BPMC), Cambridge, Mass.
Business: Cancer
Date completed: 2015-04-29
Type: IPO
Raised: $146.6 million
Shares: 8.1 million
Price: $18
Shares after offering: 25.8 million
Underwriters: Goldman Sachs; Cowen; JMP Securities; Wedbush
Overallotment: 1.2 million

**CRISPR Therapeutics AG**, Basel, Switzerland
Business: Gene/Cell therapy
Date completed: 2015-04-29
Type: Venture financing
Raised: $29 million
Investors: SROne; Celgene Corp.; New Enterprise Associates; Abingworth Management; Versant Ventures

**cytena GmbH**, Freiburg, Germany
Business: Supply/Service
Date completed: 2015-04-29
Type: Venture financing
Raised: €1.1 million ($1.2 million)
Investors: High-Tech Gruenderfonds; private investor

**GW Pharmaceuticals plc** (LSE:GWP; NASDAQ:GWPH), Salisbury, U.K.
Business: Neurology, Autoimmune
Date completed: 2015-04-28
Type: Follow-on
Raised: $179.2 million
Shares: 1.6 million
Price: $112
Shares after offering: 21.4 million
Underwriters: Morgan Stanley; BofA Merrill Lynch; Cowen; Piper Jaffray
Overallotment: 240,000

Note: Each ADS represents 12 ordinary shares. All figures are in ADS.

**Horizon Pharma plc** (NASDAQ:HZNP), Dublin, Ireland
Business: Autoimmune, Inflammation, Neurology
Date completed: 2015-04-24
Type: Private placement of senior notes
Raised: $475 million
Investor: Institutional investors

Note: The unsecured notes bear 6.625% interest and mature on May 1, 2023. Horizon also plans to secure a $400 million term loan facility.

**InCarda Therapeutics Inc.**, San Francisco, Calif.
Business: Cardiovascular, Drug delivery
Date completed: 2015-04-28
Type: Venture financing
Raised: $5 million
Investors: Morningside Venture Investments; and other undisclosed investors

Note: InCarda raised over $5 million in a series A financing. The company may raise an additional $1.5 million.

**Inovio Pharmaceuticals Inc.** (NASDAQ:INO), Blue Bell, Pa.
Business: Cancer, Infectious
Date completed: 2015-04-30
Type: Follow-on
Raised: $76 million
Shares: 9.5 million
Price: $8
Shares after offering: 70.2 million

Underwriters: Piper Jaffray; Stifel, Nicolaus; H.C. Wainwright; Brean Capital; Maxim Group
Overallotment: 1.4 million

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

Business: Endocrine/Metabolic
Date completed: 2015-04-27
Type: Venture financing
Raised: $225 million
Placement agent: Morgan Stanley

Note: The financing is convertible limited recourse notes. The undisclosed investors will receive a 1.5% royalty on future global sales of diabetes compound ITCA 650. Investors also have the option to convert their royalty interests into Intarcia shares within two years of ITCA 650's approval or by the end of 2019, whichever comes later, based on a company valuation of $5.5 billion.

**Lombard Medical Inc.** (NASDAQ:EVAR), Irvine, Calif.

Business: Cardiovascular
Date completed: 2015-04-28
Type: Debt financing
Raised: $11 million
Investor: Oxford Finance

Note: Lombard Medical drew down $11 million from a new $26 million loan facility. The company has the option to draw down $10 million based on near-term revenue milestones. The remaining $5 million will be available after reaching another revenue target.

**Mirna Therapeutics Inc.**, Austin, Texas

Business: Cancer
Date completed: 2015-04-30
Type: Venture financing
Raised: $41.8 million
Investors: Baxter Ventures; Eastern Capital; Sante Ventures LLC; Morningside Venture Investments; Rock Springs Capital; Celgene Corp.; Sofinnova Partners; New Enterprise Associates; Pfizer Venture Investments; Osage University Partners; Correlation Ventures; and other investors

**MyoKardia Inc.**, San Francisco, Calif.

Business: Cardiovascular
Date completed: 2015-04-30
Type: Venture financing
Raised: $46 million
Investors: Casdin Capital LLC; Cormorant Asset Management; Perceptive Life Sciences Fund; BridgeBio; Sanofi; and an undisclosed investor

**Novogen Ltd.** (ASX:NRT; NASDAQ:NVGN), Hornsby, Australia

Business: Cancer, Neurology
Date completed: 2015-04-29
Type: Private placement
Raised: A$15.5 million ($12.1 million)
Shares: 51.8 million
Price: A$0.30
Shares after offering: 338.1 million
Placement agent: H.C. Wainwright
Investor: Institutional investors

Note: Investors also received six-month options to purchase up to 51.8 million shares at A$0.30 and five-year options to purchase up to 25.9 million shares at A$0.40.

**OncoGenex Pharmaceuticals Inc.** (NASDAQ:OGXI), Bothell, Wash.

Business: Cancer
Date completed: 2015-04-30
Type: Private placement of units
Raised: $2 million
Units: 956,938
Price: $2.09 (unit)
Shares after offering: 23.6 million
Investor: Lincoln Park Capital Fund LLC

Note: The series A-1 units were sold under a new, two-year, $18 million share purchase agreement and comprise a share and a five-year warrant to purchase 0.25 shares, with each whole warrant exercisable at $2.40.

**Pamlico BioPharma Inc.**, Oklahoma City, Okla.

Business: Antibodies, Infectious
Date completed: 2015-04-29
Type: Venture financing
Raised: $2.2 million
Investors: Accele Venture Partners L.P.; Oklahoma Seed Capital Fund

**Paratek Pharmaceuticals Inc.** (NASDAQ:PRTK), Boston, Mass.

Business: Infectious, Dermatology, Neurology
Date completed: 2015-04-29
Type: Follow-on
Raised: $70.1 million
Shares: 2.9 million
Price: $24.50
Shares after offering: 17.3 million
Underwriters: Leerink Partners; Guggenheim Securities; Ladenburg Thalmann; BTIG; Cantor Fitzgerald
Overallotment: 429,000

**PEP-Therapy S.A.S.**, Evry, France

Business: Cancer

Date completed: 2015-04-27
Type: Venture financing
Raised: €1.3 million ($1.4 million)
Investors: Seventure Partners; private investor

**Protea Biosciences Group Inc.** (OTCQB:PRGB), Morgantown, W.Va.

Business: Diagnostic, Supply/Service
Date completed: 2015-04-27
Type: Private placement of convertible preferred stock and warrants
Raised: $7.4 million
Shares outstanding prior: 66.6 million
Placement agent: Laidlaw
Investors: Existing investors; accredited investors

Note: Investors also received three-year warrants.

**Rapid Micro Biosystems Inc.**, Lowell, Mass.

Business: Supply/Service
Date completed: 2015-04-29
Type: Venture financing
Raised: $25 million
Investors: Shenzhen Hepalink Pharmaceutical Co. Ltd.; Richard King Mellon Foundation; Kleiner Perkins Caufield & Byers; Longitude Capital Management; Quaker Partners; TPG Biotech; TVM Capital

**Theraclone Sciences Inc.**, Seattle, Wash.

Business: Infectious, Inflammation
Date completed: 2015-04-30
Type: Venture financing
Raised: $3.1 million
Investors: Wellcome Trust; existing investors

Note: Theraclone raised $3.1 million of a planned $4.4 million series C round.

**Viking Therapeutics Inc.** (NASDAQ:VKTX), San Diego, Calif.

Business: Endocrine/Metabolic, Musculoskeletal, Hematology
Date completed: 2015-04-29
Type: IPO
Raised: $24 million
Shares: 3 million
Price: $8
Shares after offering: 9.2 million
Underwriters: Laidlaw; Feltl
Overallotment: 450,000

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## PROPOSED OFFERINGS

**Affimed N.V.** (NASDAQ:AFMD), Heidelberg, Germany

Business: Cancer, Inflammation, Antibodies
Date announced: 2015-04-27
Type: Follow-on
To be raised: Up to $40.3 million
Shares: TBD
Price prior: $11.72
Underwriters: Jefferies; Leerink Partners; BMO Capital Markets

**Karo Bio AB** (SSE:KARO), Stockholm, Sweden

Business: Endocrine/Metabolic
Date announced: 2015-04-29
Type: Rights offering
To be raised: Up to SEK229.9 million ($26.6 million)
Shares: 229.9 million
Price: SEK1
Shares outstanding prior: 676.3 million
Investor: Existing investors

Note: Shareholders are eligible to purchase one shares for every three held.

**Novogen Ltd.** (ASX:NRT; NASDAQ:NVGN), Hornsby, Australia

Business: Cancer, Neurology
Date announced: 2015-04-21
Type: Rights offering
To be raised: Up to A$16.9 million ($13.2 million)
Shares: 56.4 million
Price: A$0.30
Shares outstanding prior: 338.1 million
Investor: Existing investors

Note: Shareholders are eligible to purchase one shares for every six held. Investors will receive six-month options to purchase up to 56.4 million shares at A$0.30 and five-year options to purchase up to 28.2 million shares at A$0.40.

**Syngene International Ltd.**, Bangalore, India

Business: Supply/Service
Date announced: 2015-04-22
Type: IPO
To be raised: TBD
Shares: 22 million
Price: TBD
Underwriters: Axis Financial Group; Credit Suisse; Jefferies

Note: The subsidiary of Biocon Ltd. (NSE:BIOCON; BSE:BIOCON, Bangalore, India) is seeking to list its shares on the Bombay Stock Exchange and the National Stock Exchange of India.

Biocon, which holds an 84.5% stake in Syngene, is selling up to 22 million shares of Syngene.

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## AMENDED OFFERINGS

**Adaptimmune Therapeutics plc**, Abingdon, U.K.

Business: Cancer, Infectious, Gene/Cell therapy
Date announced: 2015-04-27
Type: IPO
To be raised: Up to $159.4 million
Shares: 9.4 million
Price: $15-$17
Underwriters: BofA Merrill Lynch; Cowen; Leerink Partners; Guggenheim Securities
Overallotment: 1.4 million

Note: Adaptimmune amended its IPO on NASDAQ and now plans to sell 9.4 million ADSs at $15-$17. Each ADS represents six ordinary shares. Last month, the company filed to raise up to $150 million.

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

Business: Dermatology
Date announced: 2015-04-27
Type: IPO
To be raised: Up to $54.6 million
Shares: 3.9 million
Price: $12-$14
Underwriters: Stifel, Nicolaus; RBC Capital Markets; JMP Securities; Needham
Overallotment: 585,000

Note: Anterios amended its IPO on NASDAQ and now plans to sell 3.9 million shares at $12-$14. The company filed to raise up to $57.5 million in March.

**aTyr Pharma Inc.**, San Diego, Calif.

Business: Hematology, Inflammation, Cancer
Date announced: 2015-04-27
Type: IPO
To be raised: Up to $80.4 million
Shares: 5.4 million
Price: $13-$15
Underwriters: JPMorgan; Citigroup; BMO Capital Markets; William Blair
Overallotment: 804,000

Note: aTyr amended its IPO on NASDAQ and now plans to sell 5.4 million shares at $13-$15. Last month, the company proposed to raise up to $86.3 million.

**BiondVax Pharmaceuticals Ltd.** (Tel Aviv:BNDX), Ness Ziona, Israel

Business: Infectious
Date announced: 2015-04-28
Type: Follow-on
To be raised: Up to $11.5 million
Shares: 1.4 million
Price prior: NIS0.66
Underwriter: Aegis Capital
Overallotment: 210,000

Note: BiondVax amended its offering on NASDAQ and now plans to sell up to 1.4 million ADSs and four-year warrants to purchase up to 1.4 million ADSs. Each ADS represents 40 ordinary shares. Last December, the company filed to raise up to $10 million.

**Boston Therapeutics Inc.** (OTCQB:BTHE), Manchester, N.H.

Business: Endocrine/Metabolic, Inflammation, Chemistry
Date announced: 2015-04-28
Type: Best efforts offering
To be raised: Up to $5 million
Shares: 25 million
Price prior: $0.40
Shares outstanding prior: 38.6 million

Note: Boston Therapeutics amended its self-underwritten, best efforts offering and now plans to sell up to 25 million shares. For each share purchased, investors will receive five-year warrants to purchase 0.5 shares, with each whole warrant exercisable at $0.30. In February, the company amended the offering to sell up to 6.5 million shares. Last August, the company filed to raise up to $10 million.

**Collegium Pharmaceutical Inc.**, Canton, Mass.

Business: Drug delivery, Neurology, Inflammation
Date announced: 2015-04-27
Type: IPO
To be raised: Up to $81.2 million
Shares: 5.8 million
Price: $12-$14
Underwriters: Jefferies; Piper Jaffray; Wells Fargo; Needham
Overallotment: 870,000

Note: Collegium amended its IPO on NASDAQ and now plans to sell 5.8 million shares at $12-$14. Last month, the company filed to raise up to $86.3 million.

**Gelesis Inc.**, Boston, Mass.

Business: Endocrine/Metabolic
Date announced: 2015-04-23
Type: IPO
To be raised: Up to $56 million
Shares: 4 million
Price: $12-$14
Underwriters: Piper Jaffray; Stifel, Nicolaus; Guggenheim Securities

Overallotment: 600,000

Note: Gelesis amended its IPO on NASDAQ and now plans to sell 4 million shares at $12-$14. Last month, the company filed to raise up to $60 million.

**HTG Molecular Diagnostics Inc.**, Tucson, Ariz.

Business: Genomics, Supply/Service, Diagnostic
Date announced: 2015-04-28
Type: IPO
To be raised: Up to $53.6 million
Shares: 3.6 million
Price: $13-$15
Underwriters: Leerink Partners; Canaccord; JMP Securities
Overallotment: 535,500

Note: HTG amended its IPO on NASDAQ and now plans to sell 3.6 million shares at $13-$15. The company filed to raise up to $60 million last December.

**Klox Technologies Inc.**, Laval, Quebec

Business: Dermatology
Date announced: 2015-04-27
Type: IPO
To be raised: Up to $72 million
Shares: 4.8 million
Price: $13-$15
Underwriters: UBS; Canaccord; Needham; National Bank
Overallotment: 720,000

Note: Klox amended its IPO on NASDAQ and now plans to sell 4.8 million shares at $13-$15. The company filed to raise up to $75 million in February.

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

Business: Neurology
Date announced: 2015-04-24
Type: Follow-on
To be raised: Up to $14.5 million
Units: 14,500
Price prior: $2.05
Underwriters: Maxim Group; Dawson James Securities

Note: NeuroMetrix amended its offering and now plans to sell 14,500 units. Each unit consists of a share of series B convertible preferred stock and a five-year warrant to purchase shares. Last month, NeuroMetrix amended the offering to sell up to 9.9 million shares with 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: 2015-04-28
Type: IPO
To be raised: Up to $18.5 million
Shares: 2.9 million
Price: $5.50-$6.50
Underwriters: Maxim Group; National Securities
Overallotment: 427,500

Note: OpGen amended its IPO on NASDAQ and now plans to sell 2.9 million units at $5.50-$6.50. Each unit consists of a share and a five-year warrant to purchase a share at 110% of the IPO price. In April, the company amended its IPO and proposed to sell 3.8 million shares at $8-$10. OpGen filed to raise up to $34.5 million in March. The overallotment comprises 427,500 shares and/or warrants to purchase up to 427,500 shares.

**Ritter Pharmaceuticals Inc.**, Los Angeles, Calif.

Business: Gastrointestinal
Date announced: 2015-04-24
Type: IPO
To be raised: Up to $21.8 million
Shares: 1.8 million
Price: $10-$12
Underwriters: Aegis Capital; Chardan Capital Markets; Barrington Research
Overallotment: 273,000

Note: Ritter amended its IPO on NASDAQ and now plans to sell 1.8 million shares at $10-$12. The company also added Chardan Capital and Barrington Research as underwriters. Ritter filed to raise up to $17.3 million in March.

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## OTHER FINANCIAL NEWS

**CRISPR Therapeutics AG**, Basel, Switzerland

Business: Gene/Cell therapy
Date announced: 2015-04-29

Note: CRISPR raised $35 million in a final close of a series A round, bringing the total raised to $60 million. New investor SROne led the final close while Celgene Corp. (NASDAQ:CELG, Summit, N.J.); New Enterprise Associates; and Abingworth joined founding investor Versant Ventures. The company raised $25 million in April 2014.

**Lipocine Inc.** (NASDAQ:LPCN), Salt Lake City, Utah

Business: Drug delivery
Date announced: 2015-04-29

Note: Lipocine raised $4.5 million through the sale of 697,500 shares at $6.50 to cover the overallotment from its April 24 follow-on, bringing the total raised to $34.8 million. The company, which closed Friday at $6.50, has 18.2 million shares outstanding.

## BIOCENTURY WEEK IN REVIEW

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