Viral crossroads

By Steve Usdin
Washington Editor

Now that the family of seven-year-old Josh Hardy has successfully obtained access to an experimental drug, aided by an explosion of social media support, lawmakers, industry and patients still are left grappling with the fundamental inequities and flaws of the U.S. system for granting compassionate access to investigational therapies.

The problems have existed for years, including the idiosyncrasies of who gets access to investigational drugs outside of clinical trials and the criteria companies use to make decisions that are often life-and-death.

The fact that individual companies have been left to make these decisions on an ad hoc basis inevitably fuels suspicions among patients, family members and the public about the motives for denying access.

The difference in perspectives between companies focused on gaining regulatory approval and individuals trying to save desperately ill loved ones can make mutual suspicion curdle into antagonism.

BioCentury This Week

Cover Story

Viral crossroads — The Josh Hardy case highlights the inadequacy of the process for deciding when to grant access to experimental medicines outside of clinical trials. It also may be a catalyst for change.

Josh Hardy Chronicles — While social media users may be claiming the credit, in the end Chimerix and FDA had to clear a way to provide brincidofovir to a handful of patients while opening a door for broader access via a bigger trial.

Commentary: The Equitable Pathway — It is possible to identify basic principles that should underlie a transparent system for reviewing compassionate use requests, no matter who does the assessment.

Emerging Company Profile

Going Small — ImmuSmol’s antibodies treat cancer by targeting small molecule metabolites involved in tumor immune evasion.

Building Better Binders — Indi Molecular’s protein-catalyzed capture platform produces synthetic peptides with the binding specificity and affinity of mAbs and many of the biological properties of small molecules.

Finance

Steady Hand — LSP has survived 25 years as a life sciences VC by making a few small changes to an otherwise single-minded strategy focused on investing in early stage European biotechs.

Ebb & Flow — Biotech slip-sliding away? Endocyte tops up. Ysios’ new fund. NetScientific-Breakout Labs. Also: Epigenomics; Exact Sciences; MannKind; Cellestis; Exelixis; Idera; Horizon Discovery; Zogenix, et al.

Featured links this week/A21
Stock charts & tables/A22
Company index/A16

BioCentury 100™ Indicators
Week ended 3/28/14

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Tokyo Calling

BIO Asia is less than two weeks away but there’s still time to register for this exclusive partnering forum. Details follow A23.

Shipping Up to Boston

The rEVOLUTION Symposium in Boston will examine the organization and management of R&D to uncover new disruptive models. Details follow A23.

Lace Up Your Boots

BioEquity Europe will explore what it takes for companies to be promoted to the biotech Premier League. Registration link follows A23.

See Program Notes on A5
The rise of social media as an advocacy tool now raises the prospect that medical and regulatory decisions will be tipped by a public outcry.

As the Hardy case illustrates, patients or their relatives can generate hundreds of thousands of supporters virtually overnight, along with a wave of attention on television. In the heat of a media feeding frenzy, it is impossible for a CEO to communicate the complexities of drug development and why the integrity of the regulatory approval pathway must be protected to get a drug to as many patients as possible.

And a CEO who says “no” is no match for 100,000 angry Twitter messages and death threats from angry individuals who jump on the bandwagon. The threat of demonization has led companies to be wary of individuals and groups seeking to obtain compassionate use access to their products.

While the Hardy case reflects old problems, it also may be a game-changer. The almost immediate and apparently extraordinary effectiveness of Chimerix Inc.’s brincidofovir for Josh Hardy, coupled with the power of social media to push the company to find a way to provide access, have already led other families to pursue similar campaigns (see “The Josh Hardy Chronicles,” A7).

The Hardy case also has prompted members of Congress, industry trade associations, patient advocacy groups and individual companies to reassess the need for new principles to guide compassionate access decision-making in the era of social media and patient empowerment.

Biotech industry leaders are suggesting it may be time to shift some decisions about compassionate access off the shoulders of CEOs and onto new institutions to help adjudicate requests for pre-approval access to medicines.

All of this points to the need for public consensus on a transparent pathway for making decisions about compassionate access (see “Commentary,” A9 & “Decision Tree for Compassionate Use,” A11).

### FDA procedures

The medical, ethical, business and logistical aspects of providing access to investigational drugs can be complex and contentious, but the regulatory pathway is straightforward.

While companies, patients and the media sometimes accuse FDA of preventing compassionate access to an investigational drug, data show the agency virtually never denies requests.

This does not mean patients always get access to unapproved drugs. Requests for access must be submitted by drug sponsors or with their permission. Patients cannot apply directly to FDA, and the agency will not process an application from a physician unless a sponsor is willing to provide access to its product.

That does not mean FDA always plays a passive role. Agency officials sometimes reach out to companies to encourage them to provide access to investigational drugs, according to Richard Klein, director of FDA’s Patient Liaison Program.

The agency has initiated expanded access discussions with companies based on requests from patients, media coverage and other triggers.

Biotech executives report they’ve received calls from FDA relaying requests from members of Congress for family members or constituents to receive access to investigational drugs.

FDA has used the term “compassionate access” in the past, but now it uses “expanded access to investigational drugs for treatment use.” According to guidance released in 2013, expanded access is intended “for patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives.”

The guidance lists criteria FDA applies to review expanded access applications, including a determination that the “potential benefit justifies the potential risks of the treatment use with the drug and that those risks are not unreasonable in the context of the disease or condition to be treated.”

FDA must determine that providing expanded access “will not interfere with development of the drug for the expanded access use, and that the patient cannot obtain the drug under another IND or protocol.”

To reduce impediments to expanded access, FDA does not require reporting of outcomes data.

“Expanded access is designed for regular doctors — treating physicians as opposed to research doctors — so reporting requirements are minimized,” Klein told BioCentury. FDA requires reports only about basic safety information, such as “serious and unexpected adverse events that may be related to the drug, for example liver failure,” he added.

As a result, Klein noted, FDA only has anecdotal information about the efficacy of drugs provided under expanded access.

In some cases, as with Chimerix’s brincidofovir, the agency works with companies to create a clinical trial that could lead to a new approval or expanded indication.

But while Josh Hardy’s response to brincidofovir may have been dramatic, Klein noted the feedback FDA receives suggests that patients and physicians seeking expanded access are often over-confident about the potential for experimental treatments to provide dramatic cures.

“Every now and then people will call back and say, ‘We really appreciate the help, but my mom has died,’” he said. “No one has ever called up and said, ‘I really appreciate the help, and my mom’s great.’ You would think they would be more likely to call if that happened.”

There are, however, numerous reports in the medical literature of positive responses to compassionate use treatments. For example, in 2009 German researchers reported in Blood that compassionate use of Nexavar sorafenib in five patients with acute myelogenous leukemia (AML) produced “sustained regression before and after allogeneic stem cell transplantation.”

And the first published report about the efficacy of brincidofovir recounted the dramatic rescue of a pediatric transplant patient.

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**This Week in SciBX**

**Bitter Taste for Sinus Infections** — A Penn study has shown that bitter taste agonists stimulate release of antimicrobial peptides in the sinuses, suggesting a new way to treat chronic rhinosinusitis. SciBX Table of Contents, A15.
patient with a life-threatening adenovirus infection.

Tip of the iceberg

Despite the extensive list of criteria FDA staff apply to expanded access applications, “for the most part it is not a very intense review; they are not looking for reasons not to give” expanded access, Klein said.

FDA reports that it approved 99.4% of expanded access applications submitted from October 2009 to September 2013 (see “Expanded Access Scorecard”).

Neither FDA nor any other entity keeps track of how many requests from patients and physicians for access to experimental treatments are turned down by companies.

Arthur Caplan, a bioethicist who often provides advice to hospitals and life sciences companies about compassionate use and other ethical issues, says it is likely that only a small fraction of refusals make it into the media.

“From my own experience getting calls from companies for input, the cases we see in the media are the tip of an iceberg,” he told BioCentury.

Caplan is director of the Division of Medical Ethics in the Department of Population Health at New York University’s Langone Medical Center.

Clinicians report that companies routinely deny their requests for compassionate access.

Reasons for refusal

There are two sets of reasons for companies to deny compassionate access requests: reasons the industry publicly acknowledges and reasons executives disclose.

Peter Adamson, chief of the division of clinical pharmacology and therapeutics at the Children’s Hospital of Philadelphia, told BioCentury he limits compassionate use requests to instances in which there is good evidence that an investigational drug will help a child and the potential benefits clearly outweigh risks from the underlying disease.

Nevertheless, Adamson said he has never successfully obtained compassionate use.

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### Expanded access scorecard

FDA acts on requests for expanded access when submitted by a sponsor or by a third party with the sponsor’s support. The agency approved 99.4% of expanded access applications submitted from October 2009 to September 2013. The agency did not deny any requests to amend existing INDs, which FDA calls expanded access protocols. FDA denied only 24 of the 3,792 requests it received for an expanded access IND, which is used when there is no existing IND that can be amended, or when a sponsor with an existing IND declines to be the sponsor for expanded access. For example, a company may ask a physician to serve as the sponsor of an expanded access IND. Of the 24 requests for expanded access INDs that FDA did not permit to proceed, 21 were applications for emergency use. Emergency INDs and protocols can be approved rapidly for a single patient without a written request. Intermediate-size INDs and protocols cover up to 100 patients; treatment INDs and protocols are for more than 100 patients. For the time periods below, 2010 and 2011 represent the years ended Oct. 12, while 2012 and 2013 are for the years ended Sept. 30. Source: FDA

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![Expanded access INDs chart](chart1.png)

**Expanded access INDs**

- **Emergency**
- **Single patient**
- **Intermediate**
- **Treatment**

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- **Allowed**
- **Denied**

![Expanded access protocols chart](chart2.png)

**Expanded access protocols**

- **Emergency**
- **Single patient**
- **Intermediate**
- **Treatment**

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- **Allowed**
- **Denied**
access program did not prevent approval: Aldurazyme laronidase.

Agency spokesperson Stephanie Yao told BioCentury their biggest concern is that a serious safety issue will be identified in a population that would not have been included in clinical trials. Even if it is impossible to definitively attribute the adverse event to the investigational drug, a safety incident could lead FDA to deny approval, they said.

Caplan recounted similar worries, telling BioCentury companies have told him they are concerned that adverse events in patients who receive an investigational drug outside a trial will delay or prevent drug approval.

Adamson of Children’s Hospital does not buy those arguments. He argued the fear of adverse events leads companies to inappropriately reject compassionate use requests for pediatric cancer patients.

There is a mythology that if FDA sees a serious adverse event in children it will derail development of a drug. That’s nonsense,” he said.

Moreover, Adamson said, “There is no data I am aware of that a company with a compassionate access program has experienced a delay in approval.”

Nancy Goodman, founder of patient advocacy organization Kids vs Cancer, also rejects the adverse event fears.

“Companies are often too quick to reject requests for compassionate use from kids because they have an exaggerated fear of negative attention from the death of a child on their drug,” she told BioCentury. Goodman said regulators, families and the public understand experimental drugs may not always be effective, and that safety hasn’t been fully characterized, especially in the case of cancer treatments.

FDA officials “cannot think of an example of a drug that was not approved because it was provided through compassionate use/expanded access,” agency spokesperson Stephanie Yao told BioCentury.

There is at least one example where a death in an expanded access program did not prevent approval: Aldurazyme laronidase.

According to briefing documents prepared by BioMarin Pharmaceutical Inc. and partner Genzyme Corp. for a January 2003 advisory committee meeting, Aldurazyme was provided to four patients with mucopolysaccharidosis I (MPS I) who were seriously ill and did not meet the selection criteria for participation in ongoing trials. A 10-year-old patient who was treated under a single-patient special access protocol died.

“With Aldurazyme, we did do an expanded access patient outside of the study, and the patient did die, and we included it in the safety data that was submitted in the package. And it had no apparent impact on the approval pathway,” Emil Kakkis told BioCentury.

Kakkis, now president and CEO of Ultragenyx Pharmaceutical Inc., led development of three Orphan drugs as CMO at BioMarin, including Aldurazyme.

While FDA’s briefing documents for the advisory committee meeting discuss deaths in the formal clinical program in some detail, they mention the death in the special access protocol only in a table.

“The fatal event happened outside of the study,” Kakkis said.

Aldurazyme was approved to treat MPS I in April 2003.

The product is marketed by BioMarin and Genzyme (now part of Sanofi).

Whether the fear is justified or not, Congress could make the issue disappear.

“The American people could say, “We don’t want you holding bad outcomes against the drug.’” said NYU’s Caplan. “If we want companies to be more liberal about compassionate use, we should minimize the risk exposure when a company becomes compassionate.”

Moral challenge

Companies also must consider the possibility that implementing early access could divert scarce resources from development and approval, thus delaying broader availability of a drug.

According to BIO’s Points to Consider, companies have an ethical obligation to bring drugs to market as fast as possible.

“While the case of each individual patient may be moving and compelling, very difficult decisions must be often made to ensure fair and optimal use of limited resources in order to achieve full evaluation of a drug’s safety and effectiveness as quickly as possible,” BIO elaborated in a statement released March 18.

BIO said it is essential for companies to consider whether the development and administration of a compassionate use program “will draw the attention of key company personnel and other resources away from the crucial task of getting the drug approved for a wider population.”

The competing priorities put companies between a rock and a hard place.

“The moral challenge is you have two goals that are fundamentally incompatible,” Caplan noted. “One is trying to do the...
best you can for an individual in desperate need. The other is to try and ensure that drugs, vaccines and medical devices appear for the public that are safe and known to be efficacious. To achieve the latter you can’t always do the former.”

The media oversimplify compassionate access stories by failing to note the trade-offs, according to Caplan. “It would be nice to explain to the public that many compassionate access requests involve slowing the approval process,” he said.

In an email to BioCentury, BIO EVP for Health Sara Radcliffe described the practicalities of administering a compassionate use program.

“People must be found to design the expanded access program (including some algorithm for determining who gets the product, and possibly learning about a whole new therapeutic area), communicate with FDA and other stakeholders in order to set that program up, and then administer it,” she said.

Radcliffe added: “All these steps require substantial work. In a small company, these folks are likely already wearing a couple of hats and working more than full time on the jobs for which they were hired, and may not be able to put their regular work on hold to sustain an expanded access program.”

Chimerix President and CEO Kenneth Moch, who has been at the center of the Josh Hardy story, said the compliance burdens are especially high for a small company with few employees and limited financial resources.

When a patient received access to a drug under an expanded access protocol, Moch noted, a sponsor is required to collect data on safety. “That collection has significant costs associated with it,” he said.

Moch noted the costs are not primarily financial. Rather, they relate to the time and expertise that have to be devoted to a compassionate use program — which is then not available to move a drug development program forward.

“Compassionate use is not drug development,” Moch told BioCentury. “That is the really important point that gets lost.”

Limited resources

In some cases, compassionate access decisions are further complicated because companies have limited quantities of an investigational drug. This is more likely to occur with biologics, and in the earliest stages of clinical development of small molecules.

“Companies often have to address the challenge of equitable distribution of limited drug supply to a large number of patients in need,” according to BIO’s March 18 statement. “These decisions are particularly difficult and heart-wrenching when we know the personal stories of the individual patients.”

Companies also have an ethical obligation to ensure that compassionate access is granted fairly, according to BIO.

Patient advocates argue that supply and resource limitations are not acceptable reasons to deny all compassionate access requests.

“Just because you can’t help everyone doesn’t mean you shouldn’t help someone,” Goodman told BioCentury.

“Drug development is a public good that our society has elected to distribute through the private sector. Drug companies are profit maximizing while doing something that is good for the world,” she said.

Goodman argues this social contract confers obligations on companies to make their products widely available.

“When we give monopolies there have to be really good reasons for limiting access. These companies want a monopoly right for the purpose of providing more supply, not less. They have to defend why it is appropriate to supply less, even if it is before approval,” she said.

Adamson feels that compassionate access should be built into the development programs for drugs with the potential to provide substantial therapeutic advances, certainly in Phase III and often in Phase II.

“No one is telling the company to put all your resources into compassionate access, but a well-managed compassionate ac- See next page
I’m convinced there is a better way to make treatments more widely available to terminally ill patients, including experimental drugs.”

Rep. Michael McCaul

Next steps

Beyond these arguments, the success of social media campaigns for expanded access raises questions about fairness. The questions aren’t about the motives or actions of people who turn to social media, but rather about the fairness of a system that gives preference to individuals who succeed in gaining Twitter followers and Facebook “likes” as opposed to patients and families that lack the resources and sophistication to attract media attention.

And there is a darker side to social media. Campaigns to get Josh Hardy access to brincidofovir, and a failed attempt last year to persuade BioMarin to provide ovarian cancer patient Andrea Sloan access to the company’s BMN-673 PARP inhibitor, quickly went viral. In both cases, death threats were sent to corporate executives.

FDA’s Klein is concerned that taking disputes with companies over compassionate access to the media will become the norm.

“I worry — are cases like Josh’s going to set a new standard for how patients pursue this? This is already happening; other people are doing the same thing,” he said.

Some consensus on an ethical framework for compassionate access is needed, according to Adamson. “We can’t leave it to social media.”

The Hardy and Sloan cases have prompted Congress and industry to consider whether new compassionate access policies are needed that account for the realities of social media and the movement for patient empowerment.

One of the options they should consider, according to Caplan, is creation of a third party that could make recommendations about requests for compassionate access.

Goodman would go further, arguing that a third party might be given some power over decisions.

“If we as a society think there are certain instances in which patients should have access to unapproved drugs, then the decision-maker as to who gets the drugs should be one with society’s goals as its own goals, not a company that has a fiduciary responsibility to its investors.”

Meanwhile, some biotech CEOs are considering ways to shift the decision-making off their shoulders.

“Having the company on the hook for making these very difficult decisions is not the right thing for the company, patients or regulators,” Rachel King, CEO of GlycoMimetics Inc., told BioCentury.

“If you got everyone in a room to discuss making allocations of scarce resources, they wouldn’t say leave it to the biotech CEO or whoever gets the most signatures or has the best connections to a powerful member of Congress,” said King, who also is chair of BIO’s board of directors.

“Congress is beginning to acknowledge that compassionate use has its shortcomings,” Rep. Michael McCaul (R-Texas), told BioCentury. “We recognize the importance of starting a conversation with patient advocates, industry and other stakeholders about how expanded access could be improved.”

McCaul, founder and co-chair of the Congressional Childhood Cancer Caucus, tried to help Andrea Sloan, a constituent, get access to BMN-673.

“I’m convinced there is a better way to make treatments more widely available to terminally ill patients, including experimental drugs that hold lifesaving potential when all other options have been exhausted,” McCaul said. “We also need to recognize these drugs would not exist if not for the companies that develop them, so our first priority is to do no harm to industry and to educate ourselves about industry’s concerns while we work with them to explore options.”

Meanwhile, BIO and PhRMA say they will renew their attention to compassionate access issues.

“BIO plans to expand our dialogue with FDA, patient groups and our member companies to see if improvements to the compassionate use process can be made,” Radcliffe said.

PhRMA has similar plans, according to Sascha Haverfield, VP of scientific and regulatory affairs.

“PhRMA is in the process of creating a workgroup consisting of policy, regulatory, clinical, and legal subject matter experts from member companies to improve the clarity of the expanded access process and to further educate patients and physicians about the importance of clinical trials and the appropriate role for expanded access programs,” he told BioCentury.

COMPANIES AND INSTITUTIONS MENTIONED

BioMarin Pharmaceutical Inc. (NASDAQ:BMRN), Novato, Calif.
Biotectonomy Industry Organization (BIO), Washington, D.C.
Chimerix Inc. (NASDAQ:CMRX), Durham, N.C.
GlycoMimetics Inc. (NASDAQ:GLYC), Gaithersburg, Md.
Kids v Cancer, Washington, D.C.
New York University, New York, N.Y.
Pharmaceutical Research and Manufacturers of America (PhRMA), Washington, D.C.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Ultragrenyx Pharmaceutical Inc. (NASDAQ:RARE), Novato, Calif.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.
Regulation

Josh Hardy chronicles

By Steve Usdin
Washington Editor

The Josh Hardy story puts a human face on both the lifesaving potential of compassionate use programs and the wrenching decisions company executives must make about who receives access to compounds in clinical development.

The Hardy family’s social media campaign to gain access to an experimental therapy has apparently saved the seven-year-old boy’s life.

But along the way, television news programs depicted the situation as a simple case of corporate bad behavior that was corrected by the righteous attention of the media combined with the power of millions of people who became aware of Josh Hardy and joined the campaign to save him on Twitter.

If that were the whole story, there would be no need for new policies. But in fact, the situation was more complex.

Chimerix Inc. had been providing compassionate access to brincidofovir, an antiviral to prevent cymomegalovirus and other viral infections in stem cell transplant patients, prior to beginning pivotal trials. Following dramatic results for some patients, the demand for compassionate access to the compound far outstripped the company’s ability to administer an access program.

With demand so large and too few human resources to address it, Chimerix felt it had no way to adjudicate the requests. The company also could not ethically divert all or most of its resources away from the formal development programs that are required to provide access to brincidofovir to thousands of future patients.

In this case, FDA and the company worked together quickly to craft a development program that could allow Josh Hardy and a finite number of other patients to participate in a new study, one which could lead to approval of the molecule in a second indication of adenovirus infection.

The story could just as easily have been about any of thousands of companies working on potentially lifesaving medicines. And Josh Hardy could easily have been any of thousands of patients dying from a disease with no treatment options and no possibility of enrolling in an existing trial.

The case has sparked conversations in Congress and at drug companies about creating policies that could change the way similar cases are resolved in the future (see Cover Story).

Ghost of access past

There was a period of time — before Chimerix began pivotal studies of brincidofovir (CMX001) — when the company had public funding and was able to grant compassionate access to the molecule to treat double-stranded DNA virus infections.

Brincidofovir is based on Vistide cidofovir, an IV drug marketed by Gilead Sciences Inc. to treat cytomegalovirus (CMV) retinitis in AIDS patients. Potentially fatal nephrotoxicity caused by Vistide has limited its use.

Chimerix created brincidofovir using a technology that makes it possible to create oral formulations of IV drugs with improved potency and reduced systemic exposure (see BioCentury, Feb. 24, 2003).

Using funding from HHS’s Biomedical Advanced Research and Development Authority (BARDA), Chimerix started approving compassionate use applications in 2009. CEO Kenneth Moch told BioCentury. More than 200 patients were treated under emergency INDs in the U.S. or equivalent regulations outside the U.S.

In February 2011, the Journal of Clinical Virology published a dramatic report on a 12-year-old severely immunocompromised pediatric stem cell transplant recipient who had developed an adenovirus infection — the same kind of infection Josh Hardy contracted.

Like Josh Hardy, the patient in the JCV paper was treated with Vistide, but it damaged her kidneys and had to be stopped.

The JCV paper reported that treatment with brincidofovir under an emergency IND resulted in “successful eradication” of the infection with no drug-related serious adverse events.

It concluded: “Our extremely high-risk patient exhibited complete response to treatment with CMX001.”

In December 2012 — when the BARDA contract that had funded the access program had completed — Chimerix stopped accepting emergency IND applications for compassionate use in order to focus its resources on controlled trials that were designed to lead to FDA approval, Moch told BioCentury.

In 2012 and 2013, the company completed two Phase II trials. A trial to prevent CMV disease in patients receiving hematopoietic stem cell transplant met its primary endpoint.

Another study evaluating preemptive therapy for adenovirus infection in allogeneic hematopoietic stem cell transplant patients missed its primary endpoint but showed a lower rate of mortality.

The Chimerix timetable anticipates results in 2015 from the Phase III SUPPRESS trial to prevent CMV infection in adults undergoing hematopoietic stem cell transplantation. If successful, the trial could support accelerated approval of brincidofovir.

No good options

According to Moch, if brincidofovir had been made available outside of SUPPRESS, his 54-person company would have been swamped by demands for the compound.

See next page
The company received and denied “hundreds” of requests in 2012 and 2013, including many for children, Moch said, and there would have been more requests if the medical community had not known compassionate access was no longer available.

“Most of the physicians with whom we have close contact and are working on the SUPPRESS trial know this drug is not available on a compassionate use basis, so they tend not to request it for their patients,” he said.

“Should we allow one patient to receive the drug for whatever reason, particularly based on demands from social media, there would be tremendous demand from other patients and doctors,” Moch said. “How would we say no to any other patient with any other DNA virus, not only adenovirus?”

Chimerix believed it was making the ethical choice.

“We held firm to the ethical standard that, were the drug to be made available, it had to be on an equitable basis, and we couldn’t do anything to slow down approval that will help the hundreds or thousands of Joshes,” Moch said.

“Not only could we not ethically say no to other requests coming at us, which would swamp our resources, but it would divert our capabilities from ongoing clinical trials, which would slow our ability to get our drug approved. Patients who get sick a couple of years from now would be disadvantaged. Who are we to make this decision?” he said.

Moch stressed that constraints on providing compassionate access to brincidofovir were not caused by limited drug supply, and the cost of the drug was not the limiting factor. The limitations were the time, personnel and expertise required to process applications to FDA, and especially the time and resources required to monitor adverse events.

Social media

Josh Hardy is typical of the patients who had sought compassionate access to brincidofovir.

He developed a life-threatening adenovirus infection following a bone marrow transplant. His physicians at St. Jude Children’s Research Hospital had treated it with Vistide, but were forced to stop by severe nephrotoxicity.

As it had done hundreds of times before, Chimerix denied the family’s request for brincidofovir.

What was different this time is that the Hardy family launched a social media campaign in a desperate effort to persuade the company to change its decision.

It started with a Facebook page that garnered 48 “likes” on the first day. Cancer patient advocates began spreading the word using a #savejosh Twitter hashtag, an online petition and calls to the news media.

On March 8, CNN began broadcasting reports about Josh Hardy. The family’s request for brincidofovir.

Regulation, from previous page

BioCentury, the Bernstein Report on BioBusiness

BioCentury’s mission is to provide value-added business information & analysis for life science companies, investors, academia and government on the strategic issues essential to the formation, development and sustainability of life science ventures.

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“How would we say no to any other patient with any other DNA virus, not only adenovirus?”

Kenneth Moch, Chimerix
Commentary

The equitable pathway

Compassionate access policies in the U.S. are fraying the ties between patients, and the drug companies, physicians and regulators that are essential for medical progress.

Now that the Josh Hardy case has let the social media genie out of the bottle, it is urgent that these groups, as well as lawmakers, work together to quickly create a system that is seen by the public as a fair way to adjudicate complex interests that can be both in conflict and legitimate (see Cover Story).

The result needs to be a process that is transparent so all the stakeholders understand the rules and the criteria for granting or denying access, and it must be applied in a way that the stakeholders can see the criteria have been applied objectively and with due diligence.

BioCentury has identified some basic principles that should guide responses to compassionate use requests no matter who does the answering (see "Decision Tree for Compassionate Use," A11).

Two broad ideas are at their core. First, access should be granted to as many patients who are out of options and could benefit as possible, even if access cannot be provided to all of them.

Second, when there are impediments to providing compassionate access, all the stakeholders have a responsibility to try to lift them.

The key to implementing these principles in a way that will make the outcome of tough decisions more equitable, easier to understand and therefore more acceptable, is the creation of an independent third party that can make recommendations based on a dispassionate assessment of the facts.

It also would be desirable to create sources of funding for compassionate access that can be used when provision of treatment is beyond the manufacturer’s means. Compassionate access is in the public interest, so the public should help pay for it.

Ethical framework

The principles guiding decisions about compassionate access requests are the same regardless of differences among individual requests.

The starting point is the principle that compassionate access makes the outcome of tough decisions more equitable, easier to understand and therefore more acceptable, is the creation of an independent third party that can make recommendations based on a dispassionate assessment of the facts.

Hardy, and Fox News picked up the story the next day. Celebrities and athletes with millions of Twitter followers joined the campaign. Chimerix’s email and telephones were flooded with angry demands to help Josh Hardy — including threats of violence to company management — and newspapers around the world ran stories. Over 200,000 people “liked” the Hardy’s Facebook page.

On March 10, FDA contacted Moch to discuss options for getting brincidofovir to Josh Hardy.

The next day, Chimerix announced it had reached agreement with the agency for the “immediate initiation of a pilot trial of open-label brincidofovir for the treatment of adenovirus infections in immunocompromised patients.”

In a statement, Chimerix said “Josh Hardy’s story brought to public attention the often-devastating impact of adenovirus infection, and helped accelerate a discussion between the FDA and Chimerix regarding the need for additional clinical development to assess brincidofovir’s potential in adenovirus infection.”

The trial is capped at 20 patients.

The company said FDA also “committed to work expeditiously with Chimerix on the design of a pivotal Phase III study that would be a continuation of this pilot study.”

The number of patients who will be enrolled in the Phase III trial has not been determined, according to Moch.

He told BioCentury that Chimerix “had been talking with FDA since last August on the best way to proceed on adenovirus.”

Moch added that the path Chimerix forged with FDA “may or may not be generalizable to other drugs, but for brincidofovir it helped us progress towards regulatory approval.”

A quick response

Brincidofovir started to help Josh Hardy very quickly. On March 19, his mother, Aimee Hardy, told BioCentury that following two doses given on March 12 and 15, his viral load had dropped from 250,000 copies of adenovirus per mL to 1,000 copies.

On March 25, she reported that it dropped to 100 copies and he had been transferred out of the ICU.

The creation of an open-label trial helped Josh Hardy and has given hope to the families of several other patients who have already enrolled in the trial.

And the Hardy family’s success has inspired several other families and advocates to take their causes to social media.

Friends and relatives of Nathalie Traller, a 15-year-old with the rare cancer alveolar soft part sarcoma (ASPS), have created a Facebook page and posted videos online as part of an effort to persuade companies to provide compassionate access to investigational drugs targeting programmed death 1 (PD-1).

She is ineligible for all of the current trials of PD-1 inhibitors because the studies exclude patients who are under 18 years old.

COMPANIES AND INSTITUTIONS MENTIONED

Chimerix Inc. (NASDAQ:CMRX), Durham, N.C.
Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.
St. Jude Children’s Research Hospital, Memphis, Tenn.
U.S. Department of Health & Human Services, Washington, D.C.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.
to experimental therapies should be restricted to patients with life-threatening or serious illnesses who have no acceptable alternatives.

A clinical trial is an acceptable alternative. Compassionate access should not be a ticket to avoid the risk of being randomized to standard of care or even placebo. Doing so would make it difficult, and in some cases impossible, to enroll patients in trials that are essential to determining safety and efficacy.

Patients who are eligible for a clinical trial therefore should not be granted early access, but rather should be given information about enrolling in appropriate trials.

The next question is whether granting early access could substantially slow or prevent FDA approval, which would mean slowing or denying access to the broader patient population.

In the case of Josh Hardy, FDA and Chimerix Inc. were able to create a pilot trial of the company’s brincidofovir in a new indication, which enabled the medicine to reach the boy and create a pathway to a registration study in the second setting (see “The Josh Hardy Chronicles,” A7).

But if risks to timely approval truly cannot be mitigated, compassionate access should not be granted. It is difficult to deny patients access to hope, but this must be done if providing an experimental treatment would imperil access by much larger numbers of future patients.

The next question is whether there is adequate supply of the experimental medicine to provide access to all eligible patients.

If supply is too constrained to meet demand, funds should be provided to increase supply if it is possible to do so. This could include a dedicated fund to pay for expanding production.

If supply cannot be increased even with the provision of additional money, capacity and personnel, but there is enough supply to help some patients, then an equitable access program should be created.

“Equitable” doesn’t necessarily mean equal, nor must access be random. Depending on the circumstance, priority could be given, for example, to children, or patients most likely to have a cure, or those who are sickest.

Some advocates suggest that as a matter of principle, children should have priority over adults. Certainly, children should not be put at a disadvantage relative to adults.

The last question is whether providing compassionate access would impose a substantial financial burden on a company. Here again, the focus must be on finding solutions rather than identifying obstacles.

This could include a fund to pay for the cost of producing, quality testing and distributing the compound, and to pay companies to hire additional personnel to handle the pharmacovigilance required by FDA.

Answering tough questions

Clearly, the judgments that must be made to answer many of these questions are subjective, and they are based in part on risk calculations that will be different depending on who performs them.

For example, many drug company executives believe that compassionate access exposes drug development programs to substantial regulatory risk, a contention that FDA officials and patient advocates say is exaggerated.

Decisions about the effects of compassionate access on a drug development program must give a great deal of weight to the opinions of the company that is developing a drug. But to be credible to patients, their physicians and the public, an independent entity that does not have a financial interest should render an opinion.

In addition to taking some steam out of allegations that companies are putting profits ahead of patients, input from a trusted third party would shield drug company executives from demonization.

Similarly, when supply limitations cannot be overcome, third parties — not drug companies — should step in to develop and implement fair policies for allocating experimental drugs.

In light of the Josh Hardy case and another involving ovarian cancer patient Andrea Sloan — both of which generated physical threats against company employees — the third party idea is gaining some traction among patient groups and companies, and has been mooted by New York University ethicist Arthur Caplan as well.

The specific makeup of this entity, how it should be funded and where it should be housed is a topic for discussion. It needs to have representatives of industry, patients and regulators. And it needs a mandate to call on advisors who have sufficient expertise to make science-based decisions about the appropriateness of the requested medicine for a particular patient.

Finally, the system will require some sort of appeals process. It will be harder to wage protests if the facts of the decision can be transparently reviewed and it can be confirmed the rules were applied as intended.

The notion of an appeals process also suggests that at least part of the compassionate use pathway should be addressed through law and regulation. While some of the pathway probably could be hammered out by patient groups and companies, there are several reasons why it is likely that Congress will have to step in.

First, bipartisan legislation would show that the new system reflects broad public consensus.

Second, the overall environment for providing early access to experimental therapies would be improved by passing laws that create incentives and remove disincentives to compassionate access.

For example, it may be necessary to create a statutory safe harbor so that adverse event reports from use of a compound in uncontrolled settings or in indications the sponsor isn’t seeking don’t adversely affect FDA approval.

Finally, Congress would have to authorize a public fund and allocate money towards it.

Best practices

Companies that are developing medicines have responsibilities to obtain regulatory approval as soon as possible so their products can be disseminated as rapidly and widely as is necessary.

They also have a responsibility to help people along the way, and if they lack resources needed to do so, to seek those resources.

In the meantime, every company would be well advised to adopt and make public a compassionate use policy if its experimental drugs are likely to provide meaningful benefits over existing products for
1. Is the request for a serious or life-threatening condition, without acceptable interventions or clinical trials, that is likely to be helped by the investigational intervention?
   - Deny access; provide information about alternatives and clinical trials

2. Could compassionate access substantially slow or prevent FDA approval?
   - 2a. Is it possible to mitigate the effect on approval so broader access is not delayed/prevented?
     - Yes
     - No

3. Is there sufficient supply to provide access for all eligible patients?
   - 3a. Could supply be increased with additional resources (financial, manufacturing, personnel)?
     - Yes
     - No

4. Would providing free access impose a substantial financial burden on the company?
   - No
   - Yes

   Implement compassionate use program
   Seek funds to implement compassionate use program

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Commentary, from previous page

life-threatening or serious conditions.

Some companies have already done this.

For example, the Genentech Inc. unit of Roche states that compassionate access to investigational drugs is available to patients if they have a serious, life-threatening illness, and have "exhausted all available therapies typically used to treat the disease and [they are] no longer responsive to, or able to tolerate, these treatments." Patients must also have "no other viable therapy options, including participation in ongoing relevant clinical trials."

Genentech also says it will grant compassionate access only if it has "adequate supply of the investigational medicine," and, in the U.S., if an institutional review board (IRB) at the patient’s treating hospital or clinic reviews and approves the use of the medicine for the patient.

— Unsigned Commentary represents BioCentury’s Editorial viewpoint.

COMPANIES AND INSTITUTIONS MENTIONED

- Chimerix Inc. (NASDAQ:CMRX), Durham, N.C.
- Genentech Inc., South San Francisco, Calif.
- New York University, New York, N.Y.
- Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
- U.S. Food and Drug Administration (FDA), Silver Spring, Md.
Emerging Company Profile

ImmuSmol: Going small

By Michael J. Haas
Senior Writer

Cancer cells can evade host immunity by up-regulating enzymes that produce small molecule metabolites capable of blocking T cells in the tumor microenvironment. ImmuSmol S.A.S.’s antibodies target the metabolites to restore the immune response to tumors while side-stepping problems associated with inhibiting the enzymes themselves.

Antibodies against small molecules were first developed in the 1940s, when researchers at the University of Vienna discovered that conjugating a small molecule target to a protein carrier could elicit antibodies against that target in vivo. While such antibodies found use as immunohistochecmical research tools, they have not been widely harnessed therapeutically because of technical challenges in constructing the appropriate target-carrier conjugates, ImmuSmol CEO Alban Bessede told BioCentury.

“The target molecule, which is covalently linked to the protein carrier, must be presented to the immune system in a way that elicits antibodies with high affinity and specificity for the target,” he said. “The conjugation strategy is critical because it must not alter the physical and chemical properties of the small molecule and it must expose a good epitope.”

Designing and synthesizing conjugates that elicit the desired antibodies in mice constitute ImmuSmol’s core expertise, he said.

Bessede developed antibodies against small molecules as immunohistochecmistry tools during five years of post-graduate research. In 2012, he co-founded ImmuSmol.

He said targeting enzymes that produce metabolites involved in the tumor immune response has two drawbacks: multiple enzymes can produce the same metabolite, and each enzyme regulates the production of several metabolites involved in normal cellular functions. Thus, cancer therapies that inhibit a single enzyme may be ineffective, toxic or both.

“Our antibodies aim to block a disease-related metabolite without disrupting the function of the enzyme that produces it or interfering with other metabolites on the pathway downstream of that enzyme,” Bessede said.

He added that by targeting metabolites that contribute to tumor immune evasion, “our antibodies aim to restore immune responses to the tumor without disrupting normal immune responses in the patient.”

ImmuSmol’s lead product is a mouse mAb against a metabolite of tryptophan. While the company has not disclosed the specific metabolite, it has filed a patent application covering the use of antibodies against l-kynurenine and its metabolites to treat cancer.

L-kynurenine is a tryptophan metabolite produced primarily by indoleamine 2,3-dioxygenase 1 (IDO1). Overexpression of IDO1 correlates with poor prognosis in many cancers, including colon cancer and acute myelogenous leukemia (AML). In preclinical studies, IDO1 expressed in tumors and lymph nodes converted tryptophan to metabolites that shut down tumor-targeting T cells (see SciBX: Science-Business eXchange, July 9, 2009).

At least three other companies have IDO1 inhibitors in discovery through Phase II testing to treat various cancers.

In mouse models of colorectal cancer, ImmuSmol’s lead mAb decreased tumor growth compared with vehicle without causing toxicity. Bessede said the biotech is now testing the mAb in combination with undisclosed chemotherapies and immunotherapies.

The company chose colorectal cancer as the lead indication because levels of the tryptophan metabolite are elevated in colorectal tumors and contribute to their immune evasion. “But we may expand into other tumor types later,” he said.

ImmuSmol has two other mouse antibodies in preclinical development: one against an undisclosed small molecule to treat brain cancer and leukemia, and the other against an undisclosed tryptophan metabolite to treat multiple sclerosis (MS).

The company operates on undisclosed funds from its sole investor, French retailer Schiever Group. ImmuSmol wants to raise undisclosed funds over the next year from both a corporate partnership, which it is seeking, and grants from public institutions.

The money would enable ImmuSmol to continue in vivo preclinical development of its mAbs, and a partner would eventually help humanize the lead candidates, Bessede said.

ImmuSmol has filed two other patent applications covering antibodies against an undisclosed endogenous neurotoxin involved in neuroinflammatory diseases, and an immune-based assay for quantifying metabolites.

Bessede said a forthcoming paper from ImmuSmol will describe the use of a mAb against l-kynurenine as an immunohistochecmistry tool.

Only one other company, Lpath Inc., has reported developing antibodies against small molecule targets — all of which are lipids that are not involved in tumor immune evasion. Lpath’s lead product, sphingomab, is a humanized mAb against sphingosine-1 phosphate (S1P) that inhibits angiogenesis.

The company has two formulations of sphingomab in the clinic. A systemic formulation, called Asonep, is in Phase II testing to treat renal cell carcinoma (RCC) and Phase I to treat cancer. An ocular formulation, iSONEP, is in Phase I to Phase II testing to treat multiple ophthalmic indications.

COMPANIES AND INSTITUTIONS MENTIONED

ImmuSmol S.A.S., Pessac, France
Lpath Inc. (NASDAQ:LPTN), San Diego, Calif.
Schiever Group, Avallon, France
University of Vienna, Vienna, Austria
Emerging Company Profile

Indi Molecular: Building better binders

By Emily Cukier-Meisner
Senior Writer

Indi Molecular Inc.'s protein-catalyzed capture platform produces synthetic peptides that could be used as in vivo imaging agents and in vitro diagnostics when low target immunogenicity or suboptimal pharmacokinetics limit the utility of mAbs.

Despite their limitations, mAbs are still the platform of choice for protein recognition tasks because peptide-based approaches do not consistently yield agents with antibody-like affinity and specificity.

Indi’s protein-catalyzed capture (PCC) agents mimic the binding specificity and affinity of mAbs but have biochemical properties similar to small molecules: they are more stable, easier to manufacture and can access a wider range of targets.

“We’ve been able to create a completely synthetic approach to building binding molecules,” said CEO Albert Luderer.

Luderer is also CEO of Integrated Diagnostics Inc., which develops blood-based proteomic tests to detect early stage disease. Integrated spun Indi out so the parent company could raise a B round without obligating its investors to support the two different technologies.

To create a PCC agent, Indi screens its libraries of circular pentapeptides to find an “anchor ligand” that binds the target epitope. The company then screens for a second pentapeptide that becomes spontaneously linked to the anchor peptide via in situ click chemistry when both are bound to the same target.

In situ click chemistry is a synthetic method in which two molecules with appropriate reacting groups are spontaneously linked when they are simultaneously bound to a target that brings them close together and orients them correctly.

“The target you’re seeking to build a reagent against catalyzes the ultimate binding element that you build,” said Luderer.

The company can keep adding peptides to the PCC to reach the desired binding affinity or improve selectivity. Luderer said the anchors alone may have binding affinities of 20 nM, and each added peptide improves affinity by 5-10x.

Adding peptides also may improve selectivity by increasing the surface area of a target engaged by the molecule while decreasing affinity for off-target proteins.

Luderer added that PCCs can be labeled in vivo with fluorophores during synthesis, which is more consistent than labeling an antibody after its expression.

Unlike antibodies, which are generated by an immune response, PCCs can target poorly or non-immunogenic surfaces, such as certain retroviral proteins.

Luderer said Indi’s peptide libraries contain only D-amino acids, the right-handed form not found in nature. This reduces PCC agents’ immunogenicity and increases stability because neither the immune system nor proteases recognize them, which is important for in vivo imaging.

Indi’s most advanced in vivo imaging program is an anti-VEGF PCC. The company and researchers at the University of California, Los Angeles’ Crump Institute for Molecular Imaging are using the agent to image human xenograft tumors in mice.

Luderer said the work to date suggests the anti-VEGF PCC may concentrate at the target and wash out of non-target tissues within minutes of intravenous injection, an appropriate timescale for in vivo molecular imaging. In contrast, mAbs can take days to reach this equilibrium.

PCCs also have properties that could make them suitable for therapeutic use.

Luderer said typical PCCs contain 10-15 amino acids and have a mass of about 3.5 kD — roughly one-fortieth a mAb’s size. He said antibodies are large compared to their binding surface, which limits their activity to physically obstructing the target site. Almost all of a PCC binds its target, which lets Indi engineer in more subtle activity.

“We can create PCCs that either turn on or turn off a phosphorylation site. That’s an allosteric modulation capability,” he said.

The company prefers to partner out its programs for diagnostic and/or therapeutic applications, rather than developing products itself.

In addition to VEGF, Indi is also working on HIV gp41 and p24 proteins, falciparum malaria lactate dehydrogenase (LDH), protein kinase B (PKB; PKBA; AKT; AKT1), protein kinase B beta (PKBB; AKT2) and K-Ras.

Luderer said it takes Indi 3-5 months to develop a PCC, which could improve with investment into high throughput capability.

Indi has exclusive rights to IP covering PCC from the California Institute of Technology plus rights from The Scripps Research Institute to use click chemistry in PCC technology.

COMPANIES AND INSTITUTIONS MENTIONED
California Institute of Technology, Pasadena, Calif.
Indi Molecular Inc., Culver City, Calif.
Integrated Diagnostics Inc., Seattle, Wash.
The Scripps Research Institute, La Jolla, Calif.
University of California, Los Angeles, Los Angeles, Calif.

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Finance

LSP’s steady hand

By Stephen Hansen
Senior Writer

When LSP-Life Sciences Partners launches a new healthcare venture fund next year it will stick to a strategy that has yielded 12 exits in the past 18 months — early stage, European drug development companies. The recent exits also highlight the firm’s decision to focus on companies ripe for trade sales and to diversify its portfolio through a trio of complementary funds.

Since its beginnings in 1988, LSP has raised a total of $1 billion in eight funds and has invested in 75 private companies. There have been 18 IPOs and 25 trade sales across seven venture funds.

Over the years, the firm has added three complementary funds, with one each focused on agbio, public companies and health economics plays. The latter are companies with products that produce demonstrable savings to the healthcare system.

According to LSP’s Joachim Rothe, maintaining a consistent team and strategy has helped the firm keep its gross internal rate of return (IRR) above 25% since inception across the first six of LSP’s private company funds. The exception is the Health Economics Fund, which closed this year and hasn’t yet had an exit.

All 12 partners have been working together for at least 10 years. “We have hardly ever had any attrition, with the only changes being additions due to the growth of the organization,” Rothe told BioCentury.

What’s more, he said, “there haven’t been any wild changes in strategy over the past 25 years. We have basically stuck to what we believe we are reasonably good at.”

That strategy has been to invest about 60% in drug development plays, with the other 40% split evenly between diagnostics and medtech.

Rothe said about one third of investments are first made at seed stage; one third at the early venture round stage, such as series A or B rounds; and one third in companies in late-stage development.

About 90% of LSP’s investments are in Europe, and LSP typically is the co-lead investor in most of its deals.

Rothe said the firm’s new fund, LSP V, has a target of €150 million ($207 million) and is expected to close before the middle of next year.

Beginnings

LSP’s roots go back to 1988, when the firm’s founder, Managing Partner Martijn Kleijwegt, headed the life sciences portfolio at the mixed fund EuroVentures Benelux.

Kleijwegt went on to raise funds independently as LSP. LSP I closed in 1998 with €55 million ($65 million), backed primarily by Benelux investors like Dutch insurer Achmea B.V.

According to Rothe, LSP I had a return on invested capital of almost 7x. The second fund, LSP II, followed two years later in 2000 with a total of €114 million ($115.8 million). Performance figures for LSP II were not disclosed.

LSP added strategic LPs in each of its next two funds. LSP III closed at €140 million ($175.2 million) in 2005, with GlaxoSmithKline plc investing. Pfizer Inc. was one of the investors in the current fund, LSP IV, which closed in 2009 at just over €90 million ($125.5 million).

Rothe said LSP III has generated a 2.4x cash-on-cash return based on 14 exits so far. Eight companies remain in the portfolio. He added that LSP IV “has also generated liquidity and is well on its way to match LSP III.”

The firm’s decision in 2006 to diversify its mix of funds has contributed to its growth, according to Rothe.

“While others have decided to only do human healthcare venture capital, we decided to diversify under the life sciences umbrella. That has helped to leverage our expertise and network,” Rothe said.

In 2006, LSP launched agbio fund LSP BioVentures, with a focus on seed, crop protection, biofuel and nutrition companies. Swiss agbio company Syngenta AG is the fund’s main investor.

LSP wouldn’t disclose the IRR for LSP BioVentures, but Rothe said the fund had had one nice exit. In November 2012, Syngenta acquired portfolio company Pasteuria Bioscience Inc. for $86 million plus up to $27 million in deferred payments.

Rothe said LSP decided to launch the fund because “we realized that our deal flow and capabilities developed in the human life sciences could easily be leveraged in the adjacent plant space,” as the technologies and regulatory processes were similar.

In 2008, LSP partnered with Dutch asset manager APG to establish the LSP Life Sciences Fund, which invests in public companies. In 2011, the open-ended fund was listed on Euronext. Since inception, LSP Life Sciences Fund has had an annualized return of almost 30%.

Rothe said LSP saw the public markets as an area with less competition in Europe and an opportunity to further diversify LSP’s funds while remaining in the life sciences space.

In 2012, LSP launched its third complementary vehicle, LSP Health Economics Fund, with Achmea as the cornerstone investor. The fund’s primary mandate is to invest in life science companies that improve patient health and reduce healthcare costs. In March, the fund had a final close of €112 million ($154.3 million) (see BioCentury, March 10).

Keys to success

The firm also has made some tactical changes. In particular the 2008 financial crisis prompted LSP, like many of its peers, to focus on shaping portfolio companies into acquisition targets.
Teaching translation

Although public-private partnerships and tech transfer offices provide paths for commercializing academic discoveries, many ideas languish because researchers lack the experience to navigate translation. Several universities are starting programs that help, but bridging the mindset differences between academia and industry is challenging.

TARGETS & MECHANISMS

Insights into ependymoma

Two independent studies have revealed targets for previously intractable ependymoma tumors: a fusion protein and epigenetic modifiers, respectively. The therapeutic potential of the targets remains to be established.

THE DISTILLERY

This week in therapeutics

Stabilizing ADORA2a agonists with IgG Fc conjugation to counter autoimmune disease; combining GH1 with stimulation of MPL to treat thrombocytopenia; activating LTBR to eradicate HBV infection; and more...

This week in techniques

Cell-based prediction of the fraction of free, unbound compound in brain tissue; synthetic LMWHs with reversible and high anticoagulation activity; morning cortisol and self-reported depression symptoms to predict risk of major depressive disorder in adolescent males; and more...

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FINANCE, from previous page

“Experience tells us that IPO windows are the exception rather than the norm,” said Rothe. Thus, the firm sees trade sales as the more steady path to liquidity.

The firm has seen a handful of its companies go public, including Prosensa Holding N.V. and Celladon Corp.

In June 2013, Duchenne muscular dystrophy (DMD) play Prosensa raised $89.7 million. In January, cardiovascular company Celladon raised $50.6 million.

Exceptions aside, the focus on trade sales means most companies LSP looks at have to have a specific product opportunity.

“There have to be tangible product candidates that our research shows someone will want to acquire in a few years,” said Rothe.

He credits the focus on trade sales, combined with a “bit of luck,” to LSP’s dozen exits in the past 18 months, which is almost the same number of exits LSP had in the prior six years (see “LSP exits,” A16).

LSP’s most recent exit was Activaero GmbH. The firm took its original stake in 2011. At the time, the drug delivery play marketed its Akita Jet inhalation system to increase the deposition efficiency of inhaled therapeutics.

This month, Activaero was acquired by Vectura Group plc for €130 million ($180.6 million).

Rothe said LSP’s investment in Okairos AG, which was sold to GSK last year, was one of LSP’s “best trade sales ever.” GSK acquired the vaccine company for €250 million ($323 million), giving investors almost an 11x return on the $30 million Okairos had raised since it was founded in 2007.

LSP was one of the founding investors in Okairos after the company was spun out of Merck & Co. Inc. with a lead HCV vaccine program in Phase II development.

Another recent exit was Syntaxin Ltd. LSP first invested in the company’s £16 million ($32.8 million) series B round in 2007. At the time, Syntaxin’s lead program was SXN1187, a recombinant therapeutic protein that was in preclinical development to treat respiratory diseases.

Last year, Syntaxin was acquired by its partner Ipsen Group for €28 million ($36.6 million) in cash up front and up to €130 million ($169.8 million) in milestones.

Although there are a few exceptions, Rothe said platform plays can be hard to sell. If there is not a specific product opportunity early on, “then we are hesitant,” he said.

LSP invested in the CHF6 million ($4.9 million) series A round of platform antibody company 4-Antibody AG in 2006. In January, cancer play Agenus Inc. acquired 4-Antibody for $10 million in stock, with contingent payments that could exceed $40 million.

COMPANIES AND INSTITUTIONS MENTIONED

Achmea B.V., Zeist, the Netherlands
Agenus Inc. (NASDAQ:AGEN), Lexington, Mass.
Celladon Corp. (NASDAQ:CLDN), San Diego, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Ipsen Group (Euronext:IPN; Pink:IPSEY), Boulogne-Billancourt, France
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Pfizer Inc. (NYSE:PFZ), New York, N.Y.
Prosensa Holding N.V. (NASDAQ:RNA), Leiden, the Netherlands
Syngenta AG (SIX:SYNN; NYSE:SYT), Basel, Switzerland
Vectura Group plc (LSE:VEC), Chippenham, U.K.
LSP exits

LSP-Life Sciences Partners has had 12 exits in the past 18 months, almost the same number as in 2006-11. *Sources: LSP; BCIQ: BioCentury Online Intelligence*

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<td>Respiratory compounds based on its nebulization-based drug delivery technology</td>
<td>Acquired by Vectura Group plc (LSE-VEC)</td>
<td>€130M ($180.6M) comprising €95M ($132M) in cash and stock and €35M ($48.6M) in a deferred cash payment; also up to €6M ($8.3M) tied to future deals involving Activaero’s technologies</td>
<td>Mar-14</td>
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<tr>
<td>Celladon Corp. (NASDAQ:CLDN)</td>
<td>Lead program Mydicar gene therapy targeting ATPase Ca++ transporting cardiac muscle slow twitch 2 (ATP2A2; SERCA2A) in Phase II for heart failure</td>
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</tr>
<tr>
<td>4-Antibody AG</td>
<td>Human antibody drug candidates using its Retrocyte Display technology</td>
<td>Acquired by Agenus Inc. (NASDAQ:AGEN)</td>
<td>$10M in stock plus contingent payments in cash or stock that may exceed $40M</td>
<td>Jan-14</td>
</tr>
<tr>
<td>Affectis Pharmaceuticals AG</td>
<td>Compounds for neurodegenerative and neuroinflammatory diseases</td>
<td>Acquired by LDC Beteiligungen UG</td>
<td>Not disclosed</td>
<td>Dec-13</td>
</tr>
<tr>
<td>Syntaxin Ltd.</td>
<td>Compounds based on botulinum toxin biology</td>
<td>Acquired by Ipsen Group (Euronext:IPN; Pink:IPSEY)</td>
<td>€28M ($36.6M) up front plus €130M ($169.8M) in milestones</td>
<td>Jul-13</td>
</tr>
<tr>
<td>Kreatech Diagnostics</td>
<td>Provider of DNA fluorescent in-situ hybridization (FISH) probes and target labeling reagents for microarrays</td>
<td>Acquired by Leica Microsystems GmbH</td>
<td>Not disclosed</td>
<td>Jul-13</td>
</tr>
<tr>
<td>Prosensa Holding N.V. (NASDAQ:RNA)</td>
<td>RNA-based therapeutics for rare neuromuscular and neurodegenerative disorders</td>
<td>IPO</td>
<td>Raised $89.7M; $466.7M postmoney valuation</td>
<td>Jun-13</td>
</tr>
<tr>
<td>Okairos AG</td>
<td>Genetic vaccines for infectious diseases</td>
<td>Acquired by GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)</td>
<td>€250M ($323M) in cash</td>
<td>May-13</td>
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<tr>
<td>OctoPlus N.V.</td>
<td>Injectable compounds using its proprietary drug delivery technologies</td>
<td>Acquired by Dr. Reddy’s Laboratories Ltd. (NYSE:RDY)</td>
<td>€27.4M ($35.7M) in cash</td>
<td>Feb-13</td>
</tr>
<tr>
<td>Attune Foods</td>
<td>Organic cereal maker</td>
<td>Acquired by Post Holdings (NYSE:POST)</td>
<td>Not disclosed</td>
<td>Dec-12</td>
</tr>
<tr>
<td>Pasteuria Bioscience Inc.</td>
<td>Nematicides based on natural microbe Pasteuria</td>
<td>Acquired by Syngenta AG (SIX:SYNN; NYSE:SYT)</td>
<td>$113M including additional deferred payments of up to $27M</td>
<td>Nov-12</td>
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<tr>
<td>BMEYE B.V.</td>
<td>Non-invasive technology for advanced hemodynamic monitoring</td>
<td>Acquired by Edwards Lifesciences Corp. (NYSE:EW)</td>
<td>€33M ($42M)</td>
<td>Oct-12</td>
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</tbody>
</table>
Sector-specific concerns plus an investor rotation out of growth stocks have sent biotech shares tumbling. Buysiders think the slide is a healthy correction rather than a sign the dance music has stopped.

The iShares Nasdaq Biotechnology (IBB) exchange traded fund hit a 52-week high of 275.4 on Feb. 25. Over the past month, however, the IBB is off 13%, the BioCentury 100 Index is off 14%, the NASDAQ Biotechnology Index is down 11% and the NYSE Arca Biotechnology Index has lost 8%.

The IBB experienced steep declines on the two trading days following a March 20 letter sent by lawmakers to Gilead Sciences Inc. (NASDAQ:GILD). The letter requested information on pricing methodology for HCV drug Sovaldi sofosbuvir (see BioCentury, March 24).

In addition to investor concerns about the sustainability of biotech drug pricing, buysiders who spoke to BioCentury said macro trends are largely to blame for the sector selloff. They said generalists have shifted money from growth sectors like biotech, Internet and social media into value sectors like utilities and telecoms.

Andrew Bogan of Bogan Associates was one of several buysiders who said biotech is in the midst of a correction. He thinks the slide is likely to be both healthy and temporary given biotech’s strong underlying fundamentals.

“Any downward move in biotech stock prices, even for a few days, would be no bad thing in my view, given last year’s revaluation of the entire sector to levels not seen in years,” Bogan said. “I don’t see this triggering any kind of serious crash, but more likely a much-needed reality check that this is a difficult, research-driven business with binary regulatory outcomes and a large amount of political involvement.”

IBB finished last week off 7% but still is in the black for 2014, as are all the biotech indices. The ETF has attracted net cash inflows of $451.2 million this year (see “IBB Fund Flows”).

Gilead is off 5% since the March 20 letter. Last week, Gilead was off $3.52 to $68.55 after EMA accepted for accelerated assessment an MAA for a fixed-dose combination of Sovaldi and ledipasvir (GS-5885) to treat chronic HCV genotype 1 infection. Gilead also released an abstract saying Sovaldi plus GS-5816 led to a sustained virologic response (SVR) four weeks after the end of treatment in 86-100% of treatment-naïve patients with HCV genotypes 1-6 infection in a Phase II trial (see B20).

— Michael Flanagan

Doubling up

Endocyte Inc. (NASDAQ:ECYT) wasted no time padding its coffers after its stock almost doubled on a nod from EMA’s CHMP for Vynfinit vintafolide and data in non-small cell lung cancer (NSCLC).

Endocyte raised $94.5 million last week through the sale of 4.5 million shares at $21 in a follow-on underwritten by Credit Suisse; Citigroup; Cowen; RBC Capital Markets; Baird; Wedbush PacGrow; and Roth Capital Partners.

Endocyte proposed the offering just days after jumping $13.53 (92%) to an all-time high of $28.17 on March 21. The stock pop translated to a $489.5 million gain in market cap for a closing valuation of $1.1 billion. The move was even more pronounced given that the BioCentury 100 Index fell 4.5% that day.

The surge came on a double dose of good news.

CHMP backed conditional approval of Vynfinit for folate receptor-positive platinum-resistant ovarian cancer in combination with pegylated liposomal doxorubicin in patients who express the folate receptor on all target lesions.

Endocyte also announced Vynfinit plus docetaxel met the primary endpoint of improving progression-free survival (PFS) vs. docetaxel alone in the Phase IIb TARGET trial as second-line NSCLC treatment.

CHMP also backed approval of two companion diagnostics to be used with Vynfinit, which comprises folate linked to an alkaloid chemotherapy agent. In its recommendation, CHMP cited a PFS benefit with Vynfinit plus doxorubicin compared with doxorubicin alone.

The CHMP recommendation was no sure thing: the Phase II data for Vynfinit were mixed.

In 2011, Vynfinit plus doxorubicin met the primary PFS...
Ebb & Flow, from previous page

endpoint in the open-label Phase II PRECEDE-ENT trial. The PFS analysis was done by study investigators. Almost a year later, Endocyte hit an all-time low of $3.06 after a blinded analysis by an independent committee showed Vynffinit plus doxorubicin did not significantly improve median PFS vs. doxorubicin alone.

Despite the mixed data, Merck & Co. Inc. (NYSE: MRK) paid Endocyte $120 million up front in 2012 for exclusive, worldwide rights to Vynffinit (see BioCentury, April 23, 2012).

In 2014, Endocyte expects a DSMB to complete an interim futility analysis of the confirmatory Phase III PROCEED trial in ovarian cancer. If the DSMB recommends continuing the trial, Endocyte expects to complete enrollment in early 2015.

Endocyte expects to report overall survival (OS) data in NSCLC from TARGET this year.

The stock fell $6.21 (22%) to $21.96 last week.

Separately, at least two analysts raised their price targets on the stock (see “Analyst Picks,” A21).

— Jennifer Rhodes

Fast out of gate

A few early wins in Ysios Capital’s 2008 vintage venture fund have existing LPs looking to make bigger contributions to the firm’s second fund. The Spanish firm hopes to repeat the success of Ysios BioFund I by investing in a few near-exit opportunities early in the lifetime of the new fund.

The firm is fundraising for Ysios BioFund II. The target is €100 million ($138 million), which is about a 45% increase from the Ysios BioFund I that closed at €69 million ($98.8 million) in 2008.

The firm’s Joel Jean-Mairet told BioCentury a few early exits from Ysios BioFund I allowed the firm to start returning cash to investors.

In 2009, Ysios invested in a $30 million second close of a series F round for BioVex Inc. Two years later, the cancer vaccine company was acquired by Amgen Inc. (NASDAQ:AMGN) for $425 million up front and up to $575 million in regulatory and sales milestones.

Also in 2009, Ysios participated in the €25 million ($36 million) series B round for Endosense S.A. Last year, St. Jude Medical Inc. (NYSE:STJ) acquired the medtech play for CHF159 million ($171.8 million) up front, plus up to CHF150 million ($162.1 million) in regulatory milestones.

“We had these two early exits during the investment period. That allowed us to return capital to our investors already from 2011, and every year since,” Jean-Mairet said. “That, of course, is much appreciated.”

Indeed, he said the exits are helping bring existing investors to the new fund, and prompting them to seek to invest larger sums this time around.

Like the first fund, Ysios BioFund II will invest in both early and late stage companies in drug development, diagnostics and medtech. Geographies include North America and Europe. The new fund may consider e-health opportunities.

Jean-Mairet said the fund will invest in 15 companies and will inject up to €10 million ($13.8 million) per company.

While Ysios typically has not led financings, he said it would look to take the lead more often with the new fund. He noted that Ysios will be the lead investor in the final investment for Ysios BioFund I, an undisclosed U.S. company that is expected to close in the next few months.

— Stephen Hansen

Breaking out

NetScientific plc (LSE:NSCI) hopes a deal with The Thiel Foundation’s Breakout Labs will expand the biotech IP commercialization firm’s reach in terms of geography and stage of development.

The partnership is designed to give Breakout Labs companies a launching point for securing further venture funding.

The Thiel Foundation was established and funded by Peter Thiel, the co-founder of PayPal, which is part of eBay Inc. (NASDAQ:EBAY). Aiming to simulate early stage science innovators, the foundation launched Breakout Labs in November 2011.

Breakout has awarded 16 grants to early stage start-ups, with grants topping out at $350,000.

NetScientific identifies and invests in late-stage translational research from academic institutions, with a focus on the U.S. and U.K. Under last week’s deal, the firm will purchase a convertible note for up to $250,000 in medical technology companies that receive grants from Breakout Lab and fit the firm’s portfolio.

Lindy Fishburne, co-founder and executive director of Breakout Labs, said the partners initially will co-invest in four to six companies a year. She said the partnership is aimed at helping companies move “to market-rate dollars from philanthropic dollars.”

“One of the hardest things companies deal with is getting their first outside investor,” Fishburne added. “Every dollar after that is easier than securing the first.”

NetScientific Executive Director Michael Boyce-Jacino said the firm’s selection criteria for co-investment include a focus on diagnostics. He said the firm does not invest in drug development.

Boyce-Jacino said the deal expands NetScientific’s presence in the San Francisco Bay Area and enables the firm to invest in fully formed companies.

“To date what we’ve done are mostly assets coming directly out of universities,” he said.

Recipients of Breakout Labs grants are required to pay a 3% royalty, capped at $x the original grant, once the company has $100,000 in revenue. Additionally, the value of the award converts to equity and warrants when the company completes its next round of funding.

— Lindy Fishburne, Breakout Labs

“One of the hardest things companies deal with is getting their first outside investor.”

— Lindy Fishburne, Breakout Labs

See next page
The first Breakout Labs company to receive a NetScientific investment is Cytovale Inc., which is developing a microfluidics platform to detect biophysical changes in white blood cells associated with early stages of sepsis.

Cytovale received a Breakout Labs award in November. Fishburne said NetScientific may invest in a few other companies already in the Breakout Labs portfolio, but that most of the co-investments will be forward-looking.

Breakout Labs expects to announce its first 2014 awards in April.
— Samantha McGirr

**Banker tracks**

Former ABN AMRO executive directors Maurice Laudy and Machiel van Oostveen launched healthcare advisory firm Saola Healthcare Partners. Saola’s focus includes life sciences, medtech, diagnostics, and healthcare services and distribution.

**Private equity tracks**

Thomas Lips joined Nextech Invest Ltd. as a partner. Lips will focus on private equity investments in cancer companies. He was CEO of Liechtenstein’s Centrum Bank.

**Regulatory milestones**

Alimera Sciences Inc. (NASDAQ:ALIM) gained $0.60 to $7.20 last week after resubmitting an NDA to FDA for Iluvien to treat diabetic macular edema (DME). The company said the resubmission addresses issues raised by FDA in an October complete response letter and contains a safety update. Alimera markets Iluvien in Europe.

Alimera has rights to Iluvien from pSivida Corp. (NASDAQ:PSDV; ASX:PVA), which was off $0.55 (12%) to $3.89 on NASDAQ and off A$0.44 to A$4 in Australia for the week.

Cubist Pharmaceuticals Inc. (NASDAQ:CBST) was down $5.49 to $70.10 last week after FDA reviewers provided a summary of efficacy and safety data but did not take a position on approval of Sivekto tedisolad to treat acute bacterial skin and skin structure infections (ABSSSI). The PDUFA date is June 20. FDA reviewers also provided a summary of data but did not take a position on approval of Dalvance dalbavancin (RQ-000000002) from Durata Therapeutics Inc. (NASDAQ:DRTX) for ABSSSI. The PDUFA date is May 26.

FDA’s Anti-Infective Drugs Advisory Committee is scheduled to discuss both products on Monday.

Durata was off $1.40 to $13.50 on the week.

Epigenomics AG (Xetra:ECX) fell a combined €0.87 (17%) to €5.18 on Thursday and Friday last week after the Molecular and Clinical Genetics Panel of FDA’s Medical Devices Advisory Committee voted 5-4, with one abstention, that the benefits of colorectal cancer test Epi proColon 2.0 outweigh the product’s risks.

Concerns about the test’s efficacy were what divided the panel. After the panel voted 5-5 that Epi proColon 2.0 is effective to screen patients at average risk for colorectal cancer, the panel chair voted no to break the tie. The panel was nearly unanimously that Epi proColon 2.0 is safe in the indication, voting 9-0 in favor, with one abstention.

Epigenomics lost €3.02 (37%) on the week.

Exact Sciences Corp. (NASDAQ:EXAS) was off $0.89 to $12.86 on Friday after the Molecular and Clinical Genetics Panel of FDA’s Medical Devices Advisory Committee voted 10-0 that the benefits of Cologuard outweigh the product’s risks as an adjunctive screening test in patients who are at average risk for colorectal cancer. The panel also unanimously voted that there is reasonable assurance that Cologuard, a non-invasive stool DNA test, is both safe and effective.

Exact lost $0.70 on the week.

Halozyme Therapeutics Inc. (NASDAQ:HALO) was down $0.19 to $12.11 on Friday after the European Commission approved a subcutaneous formulation of MabThera rituximab to treat follicular non-Hodgkin’s lymphoma (NHL) and diffuse large B cell lymphoma (DLBCL). Partner Roche (SIX:ROG; OTCQX: RHHBY) already markets an IV formulation of the product in the EU for NHL and DLBCL.

The subcutaneous formulation uses Halozyme’s Enhance recombinant human hyaluronidase (rHuPH20) drug delivery technology.

Halozyme lost $1.43 (11%) to $12.11 on the week.

MannKind Corp. (NASDAQ:MNKD) was off $0.37 to $4.83 on Friday after FDA reviewers said Afrezza is effective for Type II diabetes but questioned the product’s efficacy in Type I diabetes and raised potential safety concerns. The reviewers said lung cancer is a potential risk, though the reviewers did not find a causal relationship between lung cancer and Afrezza use.

The comments came in briefing documents released ahead of a Tuesday meeting of FDA’s Endocrinologic and Metabolic Drugs Advisory Committee to discuss a resubmitted NDA for Afrezza, a dry powder formulation of insulin plus an inhaler. The PDUFA date is April 15.

MannKind was off $1.04 (18%) on the week.

Medivation Inc. (NASDAQ:MDVN) lost $5.45 to $61.08 last week after Japan’s Ministry of Health, Labor and Wealth (MHLW) approved Xtandi enzalutamide to treat castration-resistant prostate cancer.
resistant prostate cancer (CRPC). The approval triggered a $15 million milestone payment to Medivation from partner Astellas Pharma Inc. (Tokyo:4503).

QRxPharma Ltd. (ASX:QRX; OTCQX:QRXPY) was off A$0.08 to A$0.79 and down $0.44 (11%) to $3.62 in the U.S. last week. FDA said its Anesthetic and Analgesic Drug Products Advisory Committee will meet on April 22 to discuss a resubmitted NDA for MoxDuo IR morphine/oxycodone to treat moderate to severe acute pain. The PDUFA date is May 25.

FDA issued a closed response letter for MoxDuo IR in August.

Rockwell Medical Inc. (NASDAQ:RMTI) lost $1.85 (13%) to $12.11 last week. The company submitted an NDA to FDA for Triferic soluble ferric pyrophosphate (SFP) to treat iron deficiency in chronic kidney disease (CKD) patients receiving hemodialysis.

United Therapeutics Corp. (NASDAQ:UTHR) fell $4.08 to $90.67 last week following an approval by Japan's Ministry of Health, Labor and Welfare (MHLW) for subcutaneous and IV Treprost treprostinil to treat pulmonary arterial hypertension (PAH). United Therapeutics already markets the formulations as Remodulin in the U.S. and EU.

Valneva SE (Euronext:VLA; VSE:VLA) lost €0.17 to €6.47 last week after Japan's Ministry of Health, Labor and Wealth (MHLW) approved an H5N1 adjuvanted pandemic influenza vaccine from Kaketsuken and GlaxoSmithKline plc (LSE:GSK; NYSE:GSK). The vaccine uses Valneva’s EB66 cell line.

Clinical milestones

Cellectis S.A. (Euronext:ALCLS) gained €1.19 (22%) to €6.48 last week after saying it plans to raise €20.5 million ($28.3 million) through the sale of 4 million shares at €5.13 in a private placement to U.S. institutional investors. The price is a 3% premium to Cellectis’ close of €4.99 on Monday, before the company proposed the offering.

Next year, the company plans to start Phase I testing of UCART19 for leukemia. The product comprises chimeric antigen receptor (CAR)-modified, CD19-targeted allogeneic T cells.

Exelixis Inc. (NASDAQ:EXEL) fell $2.54 (39%) to $3.90 on Wednesday after an independent DMC said the Phase III COMET-I trial evaluating Cometriq cabozantinib for metastatic castration-resistant prostate cancer (CRPC) did not meet criteria to support early trial unblinding. The DMC recommended continuing the trial based on a planned interim analysis of the primary overall survival (OS) endpoint.

Earlier in the week, the European Commission conditionally approved an MAA for Cometriq to treat progressive, unresectable, locally advanced or metastatic medullary thyroid cancer (MTC). Exelixis already markets Cometriq in the U.S. for the indication. Exelixis lost $2.91 (46%) to $3.38 on the week.

Idera Pharmaceuticals Inc. (NASDAQ:IDRA) had a rollercoaster ride last week.

The company fell $1.29 (21%) to $4.79 on Monday after FDA approved Otezla apremilast from Celgene Corp. (NASDAQ:CELG) to treat adults with active psoriatic arthritis. Idera’s IMO-8400 is in Phase II testing for moderate to severe plaque psoriasis — an indication for which Otezla is under FDA and EMA review.

However, Idera made up some ground on Friday, gaining $0.69 (18%) to $4.57 after reporting IMO-8400 met the primary safety endpoint and secondary endpoint of showing clinical activity in a Phase II trial in plaque psoriasis.

By the end of 2Q, Idera expects data from an expansion cohort of the trial. IMO-8400 is a toll-like receptor 7 (TLR7), TLR8 and TLR9 antagonist.

Idera lost $1.51 (25%) on the week.

Insmed Inc. (NASDAQ:INSM) fell $2.39 (13%) to $15.90 on Wednesday after reporting that Arikayce amikacin plus standard of care missed the primary endpoint vs. placebo plus SOC in the Phase II TARGET NTM (TR02-112) trial to treat treatment-resistant non-tuberculosis mycobacterial (NTM) lung infection. But at least two analysts raised their price targets on the stock, citing positive data on the secondary endpoint (see “Analyst Picks,” A21).

Insmed plans to meet with FDA and EMA to determine next steps for Arikayce in the indication.

Insmed recovered some of its losses to finish the week off $1.29 to $17.13.

MorphoSys AG (Xetra:MOR; Pink:MPSYF) was off €2.15 to €67.56 last week after partner Johnson & Johnson (NYSE:JNJ) said guselkumab (CNTO 1959) met the primary endpoint in a Phase Ib trial to treat psoriasis. This year, J&J plans to start Phase III testing in the indication.

Guselkumab was discovered using MorphoSys’ HuCAL human combinatorial antibody library.

Swedish Orphan Biovitrum AB (SSE:Sobi) was off SEK7.75 (10%) to SEK72 on Wednesday after saying Kiobrina missed the primary endpoint vs. placebo in the European Phase III LAIF trial to treat fat malabsorption in premature infants.

Based on the results, Swedish Orphan said it will not start a U.S. Phase III trial of Kiobrina in the indication. Kiobrina is a recombinant human bile salt-stimulated lipase.

Swedish Orphan lost SEK9.30 (12%) to SEK71.45 on the week.

Ebb & Flow

Rare ophthalmic disease company Applied Genetic Technologies Corp. (NASDAQ:AGTC) gained $2.76 (23%) to $14.76 in its first day of trading Thursday after raising $50 million in an IPO through the sale of 4.2 million shares at $12. The price values Applied Genetic at $160.7 million. Earlier this month, the company said it planned to sell 3.6 million shares at $13-$15.

Applied Genetic plans to start a Phase I/II trial of its lead compound in X-linked retinoschisis (XLR) late this year. Applied Genetic finished the week up $2.55 (21%) to $14.55.

Horizon Discovery Group plc (LSE:HZD) gained 34.5p (19%) to 214.5p on its first day of trading Thursday after raising £40 million ($66 million) through the sale of 2.2 million shares at 180p in an IPO on the LSE’s AIM. The price values the company at £120.5 million ($198.7 million). Last month, Horizon Discovery said it planned to raise up to £25 million ($41.6 million) in the offering.

Horizon Discovery’s offerings include its Genesis gene editing platform and X-Man isogenic cell line platforms. Horizon finished the week up 24p (13%) to 204p.

Karyopharm Therapeutics Inc. (NASDAQ:KPTI) fell $1.11 (26%) to $30.96 last week after proposing to raise up to $115 million in a follow-on. Karyopharm’s selinexor (KPT-330) is in Phase II testing to treat relapsed glioblastoma multiforme (GBM) and ovarian, cervical and uterine carcinomas.

Transgene S.A. (Euronext:TNG) lost €0.75 to €11.90 last week after raising €65.5 million ($90.4 million) in a combined rights issue and private placement. The immunotherapy play...
raised €45.5 million ($62.8 million) through the sale of 4.6 million shares in the rights issue and €20 million ($27.6 million) through the sale of 2 million shares in the private placement. The shares were sold at €10, a 26% discount to the company’s close of €13.53 on Feb. 27, before Transgene said it planned to raise €45.5 million in a rights issue.

Early this summer, Transgene plans to start the Phase III portion of the Phase IIb/III TIME trial evaluating TG4010 for first-line non-small cell lung cancer (NSCLC).

Zogenix Inc. (NASDAQ:ZGNX) lost $0.53 (16%) to $2.73 last week after Massachusetts Gov. Deval Patrick declared opiate addiction a public health emergency and directed state authorities to immediately prohibit the prescription or sale of Zogenix’s pain drug Zohydro ER hydrocodone bitartrate.

Zohydro is an oral, non-abuse-deterrent extended-release (ER) formulation of hydrocodone. Patrick said the ban would last until FDA approves an abuse deterrent formulation.

— Staff Writers Kevin Lehnbeuter and Samantha McGirr contributed to this week’s Ebb & Flow

### Analyst picks & changes

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<th>Company</th>
<th>Bank</th>
<th>Analyst</th>
<th>Coverage</th>
<th>Opinion</th>
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<tr>
<td>Endocyte Inc.</td>
<td>Leerink</td>
<td>Howard Liang</td>
<td>Price target</td>
<td>Market perform</td>
<td>-22%</td>
<td>$21.96</td>
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<td></td>
<td>Partners</td>
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<td>Wedbush</td>
<td>Gregory Wade</td>
<td>Price target</td>
<td>Outperform</td>
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Liang raised his target to $28 from $18 after EMA’s CHMP recommended conditional approval of Vynfinit vintafolide to treat folate receptor-positive platinum-resistant ovarian cancer in combination with pegylated liposomal doxorubicin (see “Ebb & Flow,” Ax). Endocyte also reported that Vynfinit plus docetaxel met the primary endpoint of progression-free survival (PFS) in the Phase IIb TARGET trial as second-line treatment of non-small cell lung cancer (NSCLC). Liang noted that the PFS signal was “relatively modest” and said it is too early to tell whether it will translate to an overall survival (OS) benefit in Phase III testing. Vynfinit is a folate (vitamin B9) linked to alkaloid chemotherapy agent desacetylvinblastine monohydrizide.

Wade raised his target to $65 from $23 on the Vynfinit news. He estimates modest peak sales of $430M in the EU.

<table>
<thead>
<tr>
<th>Insmed Inc. (NASDAQ:INSM)</th>
<th>H.C. Wainwright</th>
<th>Andrew Fein</th>
<th>Price target</th>
<th>Buy</th>
<th>-7%</th>
<th>$17.13</th>
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<tr>
<td></td>
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<td>Joseph Schwartz</td>
<td>Price target</td>
<td>Outperform</td>
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Fein raised his target to $30 from $25 after Insmed reported data from the Phase II TARGET NTM trial with Arikayce amikacin for treatment-resistant non-tuberculosis mycobacterial (NTM) lung infection (see B21). Arikayce missed the primary endpoint of reduction in mycobacterial density but met the secondary endpoint of culture conversion, which Fein said is a “far more clinically meaningful” endpoint. Insmed will present additional data at the American Thoracic Society meeting in May. The inhaled liposomal amikacin is administered with the eFlow Nebulizer System from Pari GmbH.

Schwartz raised his target to $30 from $22 on the “highly impressive” culture conversion data.

### Featured links this week

#### Biologics

Text of H.R. 4287 introduced into the U.S. House of Representatives, which would provide an additional five years of patent exclusivity for method of use patents covering new indications for already approved biologics (see BioCentury Extra, Tuesday, March 25).

#### CHMP

Minutes from the Feb. 17-20 meeting of EMA’s CHMP.

#### Clinical transparency

Voluntary clinical transparency principles published by the Biotechnology Industry Organization (BIO) under which member companies would be responsible for evaluating and granting requests for access to data, including patient-level data, from qualified researchers (see BioCentury Extra, Tuesday, March 25).

#### Depression

U.S. Preventive Services Task Force draft research plan on primary care screening for depression in adults.

#### Drug labeling

FDA draft guidance for the labeling of drugs and biologics approved under the accelerated approval pathway.

#### ESRD

— Report from HHS’s Office of the Inspector General recommending that CMS account for acquisition costs of drugs when annually recalculating the Medicare bundled payment rate for end-stage renal disease (ESRD) treatments (see BioCentury Extra, Tuesday, March 25).

— Text of H.R. 4302 passed by the U.S. House of Representatives, which includes a provision that would delay until 2024 the inclusion of oral drugs in CMS’s bundled payment rate to dialysis facilities for ESRD patients and extend Medicare’s sustainable growth rate (SGR) formula (see BioCentury Extra, Thursday, March 27).

#### Fecal transplant

The U.K.’s NICE guidance recommending the use of fecal microbiota transplants to treat patients with persistent *Clostridium difficile* infection that have failed to respond to antibiotics and other treatments.

#### Parkinson’s disease

Pharmaceutical Research and Manufacturers of America (PhRMA) report detailing products under development to treat PD.

See page A23
BioCentury tracks 661 issues that report prices and volume daily. The BioCentury 100 is a subset used to monitor price and volume trends.

### 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).

### Price Gains
Stocks with greatest % price increase in the week ended Mar. 28. (Priced above $2; 5,000 minimum share volume)

<table>
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<tr>
<th>Company</th>
<th>Ticker</th>
<th>$Close</th>
<th>$Chg</th>
<th>%Chg</th>
<th>Vol(00)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotec Pharmacon</td>
<td>BIOTEC</td>
<td>NOK17.2</td>
<td>NOK6.2</td>
<td>56%</td>
<td>75005</td>
</tr>
<tr>
<td>Actinium</td>
<td>ATNM</td>
<td>10.900</td>
<td>2.660</td>
<td>32%</td>
<td>1914</td>
</tr>
<tr>
<td>Celltech</td>
<td>ALCLS</td>
<td>€6.480</td>
<td>€1.190</td>
<td>22%</td>
<td>36865</td>
</tr>
<tr>
<td>Applied Genetic Tech</td>
<td>AGTC</td>
<td>14.550</td>
<td>2.550</td>
<td>19%</td>
<td>16907</td>
</tr>
<tr>
<td>Heska</td>
<td>HSKA</td>
<td>10.870</td>
<td>1.870</td>
<td>21%</td>
<td>6259</td>
</tr>
<tr>
<td>Accelerate Diag</td>
<td>AXDX</td>
<td>20.020</td>
<td>2.640</td>
<td>15%</td>
<td>11569</td>
</tr>
<tr>
<td>MEI Pharma</td>
<td>MEIP</td>
<td>11.540</td>
<td>1.460</td>
<td>14%</td>
<td>23562</td>
</tr>
<tr>
<td>Tella</td>
<td>2191</td>
<td>¥1650</td>
<td>¥199</td>
<td>14%</td>
<td>8044</td>
</tr>
<tr>
<td>Horizon Discovery</td>
<td>HZD</td>
<td>204p</td>
<td>24p</td>
<td>13%</td>
<td>326438</td>
</tr>
<tr>
<td>Keryx</td>
<td>KERX</td>
<td>16.610</td>
<td>1.770</td>
<td>12%</td>
<td>326438</td>
</tr>
<tr>
<td>JCR Pharmaceuticals</td>
<td>4552</td>
<td>¥2388</td>
<td>¥235</td>
<td>11%</td>
<td>10849</td>
</tr>
<tr>
<td>CellSeed</td>
<td>7776</td>
<td>¥1144</td>
<td>¥104</td>
<td>10%</td>
<td>5253</td>
</tr>
<tr>
<td>Cytos</td>
<td>CYTN</td>
<td>CHF2.98</td>
<td>CHF0.26</td>
<td>10%</td>
<td>2329</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Company</th>
<th>Ticker</th>
<th>$Close</th>
<th>$Chg</th>
<th>%Chg</th>
<th>Vol(00)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exelixis</td>
<td>EXEL</td>
<td>3.380</td>
<td>-2.910</td>
<td>-46%</td>
<td>966731</td>
</tr>
<tr>
<td>Aastrom</td>
<td>ASTM</td>
<td>4.060</td>
<td>-2.430</td>
<td>-37%</td>
<td>50794</td>
</tr>
<tr>
<td>Epigenomics</td>
<td>ECX</td>
<td>€5.180</td>
<td>-€3.020</td>
<td>-37%</td>
<td>24877</td>
</tr>
<tr>
<td>Advaxis</td>
<td>ADXS</td>
<td>3.130</td>
<td>-1.780</td>
<td>-36%</td>
<td>50778</td>
</tr>
<tr>
<td>Capricor Therap</td>
<td>CAPR</td>
<td>7.700</td>
<td>-2.800</td>
<td>-27%</td>
<td>661</td>
</tr>
<tr>
<td>Karyopharm</td>
<td>KPTI</td>
<td>30.960</td>
<td>-11.110</td>
<td>-26%</td>
<td>13948</td>
</tr>
<tr>
<td>Relypsa</td>
<td>RLYP</td>
<td>30.010</td>
<td>-10.080</td>
<td>-25%</td>
<td>16556</td>
</tr>
<tr>
<td>LipoScience</td>
<td>LPDX</td>
<td>3.030</td>
<td>-1.010</td>
<td>-25%</td>
<td>11538</td>
</tr>
<tr>
<td>Idera</td>
<td>IDRA</td>
<td>4.570</td>
<td>-1.510</td>
<td>-25%</td>
<td>50380</td>
</tr>
<tr>
<td>Tekmira</td>
<td>TKMR</td>
<td>19.495</td>
<td>-6.415</td>
<td>-25%</td>
<td>62269</td>
</tr>
<tr>
<td>Arrowhead</td>
<td>ARWR</td>
<td>15.620</td>
<td>-5.080</td>
<td>-25%</td>
<td>163056</td>
</tr>
<tr>
<td>Galena Biopharma</td>
<td>GALE</td>
<td>2.220</td>
<td>-0.700</td>
<td>-24%</td>
<td>227645</td>
</tr>
</tbody>
</table>

### Volume Gains
Greatest changes in volume above 5,000 shares.

<table>
<thead>
<tr>
<th>Company</th>
<th>Ticker</th>
<th>Vol(00)</th>
<th>%Chg</th>
<th>$Close</th>
<th>$Chg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotec Pharmacon</td>
<td>BIOTEC</td>
<td>75005</td>
<td>3487%</td>
<td>NOK17.2</td>
<td>NOK6.2</td>
</tr>
<tr>
<td>Heska</td>
<td>HSKA</td>
<td>6259</td>
<td>2373%</td>
<td>10.870</td>
<td>1.870</td>
</tr>
<tr>
<td>Exelixis</td>
<td>EXEL</td>
<td>966731</td>
<td>792%</td>
<td>3.380</td>
<td>-2.910</td>
</tr>
<tr>
<td>BioGaia</td>
<td>BIOG B</td>
<td>6020</td>
<td>713%</td>
<td>SEK206</td>
<td>-SEK9</td>
</tr>
<tr>
<td>Chembio</td>
<td>CEMI</td>
<td>5822</td>
<td>476%</td>
<td>3.379</td>
<td>-0.071</td>
</tr>
<tr>
<td>Advaxis</td>
<td>ADXS</td>
<td>50778</td>
<td>426%</td>
<td>3.130</td>
<td>-1.780</td>
</tr>
<tr>
<td>Epistem</td>
<td>EHP</td>
<td>457</td>
<td>367%</td>
<td>2.5p</td>
<td>327.5p</td>
</tr>
<tr>
<td>Celltech</td>
<td>ALCLS</td>
<td>36865</td>
<td>359%</td>
<td>€6.480</td>
<td>€1.190</td>
</tr>
<tr>
<td>Galexin Therap</td>
<td>GALX</td>
<td>66678</td>
<td>358%</td>
<td>15.720</td>
<td>0.100</td>
</tr>
<tr>
<td>LipoScience</td>
<td>LPDX</td>
<td>11538</td>
<td>348%</td>
<td>3.030</td>
<td>-1.010</td>
</tr>
<tr>
<td>Insmid</td>
<td>INSM</td>
<td>119462</td>
<td>329%</td>
<td>17.130</td>
<td>1.290</td>
</tr>
</tbody>
</table>

### BioCentury 100 Advance-Decline Trend
Week ended BC100 BC100 BC100 BC100 BC100 BC100
Price level Stocks gaining Gaining Declining Declining
ended vol. (00) (00) vol. (00) vol. (00)
Feb 28 5769.58 35 4552154 65 6369353
Mar 07 5685.15 46 3628540 53 6934116
Mar 14 5643.46 26 2609268 73 6556185
Mar 21 5412.73 35 4491667 65 5476357
Mar 28 4983.60 6 1066487 94 10070179

1 IPO during the week. Price change is from IPO price.
2 Includes volume from Toronto Stock Exchange
R&D

Open Innovation website launched by AstraZeneca plc (LSE:AZN; NYSE:AZN), which lists programs available for partnering and invites proposals for further development (see BioCentury Extra, Tuesday, March 25).

340B

Report from the Alliance for Integrity and Reform of 340B (AIR 340B), which said Congress should restrict the eligibility criteria for hospitals to participate in Medicare’s 340B drug discount program (see BioCentury Extra, Tuesday, March 25).

Topical products

EMA draft concept paper addressing the need for a guideline on user safety for topically administered products.

Product documentation

— Afrezza: Briefing documents for the April I meeting of FDA’s Endocrinologic and Metabolic Drugs Advisory Committee to discuss an NDA for Afrezza to treat Type I and II diabetes; from MannKind Corp. (NASDAQ:MNKD) (see BioCentury Extra, Friday, March 28).

— Cologuard: Briefing documents for the March 27 meeting of the Molecular and Clinical Genetics Panel of FDA’s Medical Devices Advisory Committee, which voted 10-0 that the benefits of Cologuard outweigh the product’s risks as an adjunctive screening test in patients who are at average risk for colorectal cancer; from Exact Sciences Corp. (NASDAQ:EXAS) (see BioCentury Extra, Thursday, March 27).

— Cometriq: EMA’s CHMP EPAR for Cometriq cabozantinib to treat progressive, unresectable, locally advanced or metastatic medullary thyroid cancer (MTC); from Exelixis Inc. (NASDAQ:EXEL) and Swedish Orphan Biovitrum AB (SSE:SOBI).

— Dalbavancin: Briefing documents for the March 31 meeting of FDA’s Anti-Infective Drugs Advisory Committee to discuss an NDA for IV dalbavancin to treat acute bacterial skin and skin structure infections (ABSSSI); from Cubist Pharmaceuticals Inc. (NASDAQ:CBST) (see BioCentury Extra, Thursday, March 27).

— Velcade: The U.K.’s NICE final appraisal determination (FAD) recommending Velcade bortezomib in combination with dexamethasone or with thalidomide and dexamethasone for induction treatment of adults with previously untreated multiple myeloma (MM) for whom high-dose chemotherapy with hematopoietic stem cell transplantation is suitable; from Johnson & Johnson (NYSE:JNJ) and Takeda Pharmaceutical Co. Ltd. (Tokyo:4502).

— Xofio: The U.K.’s NICE preliminary appraisal recommending against Xofio radium-223 dichloride to treat adults with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastases; from Bayer AG (Xetra:BayN) (see BioCentury Extra, Monday, March 24).

— Zaltrap: The U.K.’s NICE final guidance recommending against the use of Zaltrap afibercept in combination with FOFLIRI chemotherapy to treat metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen; from Regeneron Pharmaceuticals Inc. (NASDAQ:REGN) and Sanofi (Euronext: SAN; NYSE:SNY).
GETTING TO THE PREMIER LEAGUE

As Bioéquity Europe turns 15, it asks European managers and investors to review whether their companies have what it takes to play in the "Premier League."

Two plenary sessions will pose the Premier League challenge on two fronts.

Additional intimate workshops also promise to provide ‘hands-on’ guidance on what executives and investors in younger companies must do to take their game to the next level.

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The 7th Annual BioCentury/Ernst & Young Face Off
As more and more European companies look to the U.S. to raise significant growth capital, do they have what it takes to compete for the smartest money?

A Fireside Chat on Innovation with EMA
And where do their drugs, diagnostics and tools stand on the league tables for differentiation and reimbursability on a global playing field?

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Gilde Healthcare
Index Ventures
Inserm Transfert Initiative
Johnson & Johnson Innovation
LSP-Life Sciences Partners

Oxford Finance
Piper Jaffray
Roche Venture Fund

Regional Host Committee
Amsterdam BioMed Cluster/
Amsterdam Economic Board
Axon

Deloitte
Euronext
Van Campen Liem
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The 11th Annual BIO Asia International Conference, taking place April 8-9, 2014 in Tokyo, will deliver an exclusive partnering forum that brings together Asian, U.S. and European biotech and pharma companies to spark discussions ranging from research collaborations to licensing agreements and marketing deals.

Why Should You Attend BIO Asia?

• Strong international representation with 50% of all participating companies coming from Asia
• A focused audience of high-level executives and business development decision makers
• Tremendous networking opportunities to meet numerous Asian and multinational companies in one place at one time
• A world-class program that will feature key industry topics
• BIO One-on-One Partnering™ will allow you to specifically search company profiles, evaluate potential collaborations and funding opportunities, communicate directly with prospective partners, and pre-schedule private one-on-one meetings

Register Now!

For more information or to register for the event, please go to bio.org/bioasia

For customer service, contact biopartnering@bio.org
For sponsorship or exhibiting opportunities, contact Matt Lowe at mlowe@bio.org
Now in its eleventh year, the rEVOLUTION Symposium has become the place to discuss the most important strategic problems facing pharma and biotech CSOs. We will examine the organization and management of R&D to uncover new disruptive discovery and development models and assess the continued impact of pricing, reimbursement, regulation and globalization on our industry.

Topics to be covered in depth include:
- Externalization of Innovation
- Fresh Thinking about Japan
- Looking Backwards, Moving Forwards: A Discussion Among Former Large Biopharma CSOs
- Gene Therapy: The Next Frontier of Scientific and Commercial Innovation
- Global Regulatory Alignment: Impossible or a Possible Dream?
- How Payers Pick Winners and Losers for their Increasingly Restrictive Formularies

Keynote Speakers

Larry Lucchino
Mr. Larry Lucchino is the Owner of the Boston Red Sox Baseball Club LP and has been its President and Chief Executive Officer since February 2002.

Jerome Groopman, M.D. and Pamela Hartzband, M.D.
Dr. Groopman is a Dina and Raphael Recanati Professor of Medicine at Harvard Medical School, Chief of Experimental Medicine at Beth Israel Deaconess Medical Center, and staff writer for The New Yorker. Dr. Hartzband is an Assistant Professor at Harvard Medical School and Attending Physician in the Division of Endocrinology at the Beth Israel Deaconess Medical Center.

Ezekiel Emanuel, M.D.
Dr. Emanuel has a Joint Appointment at Wharton School and U Penn School of Medicine, and is the Founding Chair of the Clinical Center of the NIH.

May 7 - 9, 2014
Mandarin Oriental, Boston
776 Boylston Street
Boston, Massachusetts

For more information, please call 650-320-4529 or visit www.wsgr.com/news/revolution.

This is an invite-only event.
BioBusiness for the week ended March 28

Using BioCentury Week in Review

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And you can set your own filters to customize your personal summary of the week's corporate, clinical and financial news.

BioCentury Week in Review is a comprehensive compendium of business news for management and investors in bioscience companies. It is organized into three departments: Company News, Clinical News and Financial News.

The index on this page lists all the companies covered this week. The news items in each department are organized alphabetically by company. When more than one company is listed, the biotech company is shown first. Each brief is labeled with one or more applicable business categories from the following list:

ADMET; Agbio/Environmental; Antibodies; Autoimmune; Bioinformatics; Biomanufacturing; Biopharmaceuticals; Biosimilars; Cancer; Cardiovascular; Chemistry; Combinatorial biology; Computational chemistry/biology; Dental; Dermatology; Diagnostics; Drug delivery; Endocrine/Metabolic; Finance; Functional genomics; Gastrointestinal; Gene/Cell therapy; Generics; Genitourinary; Genomics; Hematology; Hepatic; High throughput screening; Infectious; Inflammation; Microarrays; Microfluidics; Musculoskeletal; Neurology; Nutraceuticals; Ophthalmic; Other; Pharmaceuticals; Pharmacogenetics; Proteomics; Pulmonary; Renal; Supply/Service; Transplant; Veterinary

Deals (Page B2)

Albany Molecular Res (NASDAQ:AMRI)/Cedarburg Hauser Pharma
Alnylam (NASDAQ:ALNY)/Sanofi (Euronext:SAN;NYSE:SNY)
A IM (AetkeToget:A1M)/NeuroVive (SSE:NVP)
Asahi Kasei /Vernalis (LSE:VER)
AstraZeneca (LSE:AZN; NYSE:AZN)/Sumitomo (Tokyo:4005)
Bionamics/Evotec (Xetra:EVT)
Biotie Therap (HSE:BTH1V)/UCB Group (Euronext:UCB)
CytoValve/NetScientific (LSE:NSCI)/Thiel Fndtn
Genentech/Spark Therap
Genentech/XenoPharma/Roche (SIX:ROG;OTCQX:RHBY)
Genmab (CSE:GEN; OTCBB:GMXAY)/J&J (NYSE:JNJ)
Genmab (CSE:GEN; OTCBB:GMXAY)/MAB Discovery
Guerbet (Euronext:GBT)/Sirtex Med (ASX:SRX)
IntelliCell Bio (OTCBQ:SVFC)/New York U
Manchester Pharma/Retrophin (NASDAQ:RTRX)
Myriad Genetics (NASDAQ:MYGN)/Tesaro (NASDAQ:TSRO)
NanoBio/Merck (NYSE:MRK)
NYGC/IBM (NYSE:IBM)
Pacgen Life Sci (TSX-V:PBS)/General Bio (GreTai-E:4117)
Rosetta Genomics (NASDAQ:ROSG)/Rabin Med Cntr
Singulex/Tecan (SIX:TECN)
SQI Diagnostics (TSX-V:SQD)
TapImmune (OTCBB:TPIV)/Mayo Clinic
Upsher-Smith Labs/Vertical Pharma
Ventura Group (LSE:VEC)

Sales & Marketing (Page B6)

Ambry Genetics
AstraZeneca (LSE:AZN; NYSE:AZN)
BioDelivery Sci Intl (NASDAQ:BDSI)/Quintiles (NYSE:Q)/Ashfield Mrkt Access
Biohit (HSE:BIOBV)

Otsuka/Takeda (Tokyo:4502)

Other News (Page B7)

Actavis (NYSE:ACT)/Hisamitsu Pharma (Tokyo:4530)
AstraZeneca (LSE:AZN; NYSE:AZN)
Baxter Intl (NYSE:BAX)
Gilead (NASDAQ:GILD)/Idenix Pharma (NASDAQ:IDIX)
GlaxoSmithKline (LSE:GSK; NYSE:GSK)/EMBL-EBI/Wellcome Trust Sanger Inst
IntegraGen (Euronext:ALINT)/Gustave Roussy Ins
J&J (NYSE:JNJ)
Jubilant Life Sci (BSE:530019; NSE:JUBLANT)/IDRI/Bill & Melinda Gates Fndtn
Mylan (NASDAQ:MYL)/GlaxoSmithKline (LSE:GSK; NYSE:GSK)
Sequenom (NASDAQ:SQNM)
Zymyx

Management Tracks (Page B9)

AcetRx Pharma (NASDAQ:ACRX)
Advaxis (NASDAQ:ADXS)
Akers Bio (NASDAQ:AKER; LSE:AKR)
Arno Therap (OTCQB:ARNI)
Beat BioTherap
Calico
Calithera Bio
CAP-CMV
ChemoCentryx (NASDAQ:CCXI)
Discovery Labs (NASDAQ:DSCO)
Exact Sciences (NASDAQ:EXAS)
Immunocore
Merck (NYSE:MRK)
Merck KGaA (Xetra:MRK)
miragen Therap
NPS Pharma (NASDAQ:NPS)
Osin Therap (NASDAQ:OSIR)
Pixium-Vision
Renovo (LSE:RNVO)
scPharmas
Tobira Therap

See next page
Albany Molecular Research Inc. (NASDAQ:AMRI), Albany, N.Y.
Cedarburg Hauser Pharmaceuticals Inc., Grafton, Wis.

Albany Molecular will acquire contract developer and manufacturer Cedarburg for $38.2 million in cash. Cedarburg’s core capabilities include the production of controlled substances, prostaglandins, vitamin D analogs, conjugation chemistry and inorganics for analgesic, ophthalmic and cancer therapeutic areas. Cedarburg’s stand-alone 2014 revenue is expected to be about $19 million. Albany, which is financing the deal with cash on hand, said the deal is expected to close early next month. Based on the timing of the close, Albany Molecular said the deal will add $13-$14 million to the company’s 2014 revenue. Albany Molecular provides R&D services, including drug discovery, development and manufacturing. The company reported 2013 revenue of $246.6 million. Wells Fargo advised Cedarburg.

Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY), Cambridge, Mass.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France

Sanofi’s Genzyme Corp. unit paid Alnylam $23 million to purchase 344,448 shares of Alnylam common stock at $66.88. Alnylam’s closing price on March 25, the date the shares were purchased. Under the companies’ January deal in which Alnylam granted Genzyme options to license exclusive rights outside of North America and Western Europe to Alnylam’s current “5x15” pipeline of products, Genzyme has the right to purchase additional Alnylam shares to maintain its 12% stake in the company. Alnylam’s outstanding shares increased this month when it issued 2.5 million shares, valued at $150 million, as part of a deal in which it acquired the Sirna Therapeutics Inc. subsidiary of Merck & Co. Inc. (NYSE:MRK, Whitehouse Station, N.J.) (see BioCentury, Jan. 20 & March 10).

A1M Pharma AB (AktieTorget:A1M), Lund, Sweden

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

Business: Endocrine/Metabolic

A1M and NeuroVive partnered to conduct research in mitochondrial medicine. The companies will initially utilize their “complementary scientific platforms” in ongoing research projects, after which they will explore the possibility of a “closer collaboration.” Each company will be responsible for its own costs related to the collaboration. Both companies will retain rights to existing registered IP, but future inventions from the collaboration will be jointly owned by NeuroVive and A1M. NeuroVive declined to disclose further details, and A1M declined to comment.
BioCentury Week in Review

Deals, from previous page

could not be reached for details.

A1M develops diagnostics and treatments for pre-eclampsia. The treatments are based on alpha-1 microglobulin (A1M), and the diagnostics are based on detection of raised levels of fetal hemoglobin in the mother’s blood. NeuroVive develops products to treat acute cardiovascular and neurological conditions through mitochondrial protection. NeuroVive’s CicloMulsion — a cromophor-free IV cyclosporine formulation — is in Phase III testing to treat reperfusion injury following myocardial infarction (MI), and its NeuroSTAT — a cyclosporine A lipid emulsion formulated without Cremophor EL, a stabilizing solution — is in Phase II testing to treat traumatic brain injury (TBI). NeuroSTAT has Orphan Drug designation in the U.S. and EU for TBI.

Asahi Kasei Pharma Corp., Tokyo, Japan
Vernalis plc (LSE:VER), Winnersh, U.K.
Business: Autoimmune

Vernalis will receive a £300,000 ($494,820) milestone payment under a 2013 deal with Asahi to use Vernalis’ fragment and structure-based drug discovery platform to discover low molecular weight compounds against an undisclosed target for rheumatoid arthritis (RA) and other autoimmune diseases. The milestone is the first under the deal. The companies are not disclosing further details.

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Sumitomo Chemical Co. Ltd. (Tokyo:4005), Tokyo, Japan
Business: Pharmaceuticals

AstraZeneca purchased the 20% stake of its AstraZeneca K.K. Japanese subsidiary owned by Sumitomo Chemical for ¥10 billion ($98 million). AstraZeneca now owns 100% of the subsidiary. The pharma said the purchase reinforces its focus on Japan as a key growth platform.

Bionamics GmbH, Hamburg, Germany
Evotec AG (Xetra:EVT), Hamburg, Germany
Business: Neurology, Autoimmune

Evotec acquired asset management company Bionamics for an undisclosed amount in cash. Bionamics will be eligible for undisclosed milestones. Bionamics focuses on translating academic innovations to assets for the biotech and pharma industry and manages the NEU2 consortium, which focuses on the development of therapies for multiple sclerosis and neurological diseases. Members of the consortium include Merck KGaA (Xetra:MRK, Darmstadt, Germany); Evotec; European ScreeningPort GmbH (Hamburg, Germany); and the University Medical Center Hamburg-Eppendorf (Hamburg, Germany). Evotec said the MS therapy is in early stage development, but declined to disclose further details.

Biotie Therapies Corp. (HSE:BTH1V), Turku, Finland
UCB Group (Euronext:UCB), Brussels, Belgium
Business: Neurology

UCB terminated an amended 2010 deal with Biotie granting UCB exclusive, worldwide rights to Biotie’s tozadenant (SYN115), which is in development for Parkinson’s disease. UCB said the decision was based on an assessment of the company’s clinical pipeline and preclinical opportunities and does not reflect any concerns regarding tozadenant’s safety or efficacy. UCB said the termination will lead to a one-time write-off of about €40 million ($55.2 million) to the company’s

Clinical News, from previous page

Preclinical Results (Page B27)

Novogen (ASX:NRT; NASDAQ:NVGN)

Clinical Status (Page B27)

AbbVie (NYSE:ABBV)/Eisai (Tokyo:4523)
Agiros Pharma (NASDAQ:AGIO)
Alkermes (NASDAQ:ALKS)
Antisense Therap (ASX:ANP)/Isis Pharma (NASDAQ:ISIS)
Ariad Pharma (NASDAQ:ARIA)
BioMarin Pharma (NASDAQ:BMRN)/Catalyst Pharma Ptnrs (NASDAQ:CFRX)/Jazz Pharmas (NASDAQ:JAZZ)
bluebird bio (NASDAQ:BLUE)
Cancer Research UK
Celator Pharma (NASDAQ:CPXX)
Cortice Bio
CymaBay Therap (OTCBB:CYMA)
Cytokinetics (NASDAQ:CYTK)/Astellas Pharma (Tokyo:4503)
Cytori Therap (NASDAQ:CYTX; Xetra:XMPA)
CytRx (NASDAQ:CYTR)
e-Therapeutics (LSE:ETX)
Exelixis (NASDAQ:EXEL)
Fate Therap (NASDAQ:FATE)
FibroGen/Astellas Pharma (Tokyo:4503)/

AstraZeneca (LSE:AZN; NYSE:AZN)
Hua Med/Roche (SIX:ROG; OTCQX:RHHBY)
Kamada (Tel Aviv:KMDA; NASDAQ:KMDA)/Pari
Kinex /PharmaEssentia/Hanmi (KOSDAQ:128940)
Mast Therap (NYSE-M:MTX)
Merck KGaA (Xetra:MRK)
NovoMedica/Eddingpharm/Syndax Pharmas/Bayer (Xetra:BYAN)
Novartis (NYSE:NVS; SIX:NOVN)
Portola Pharmas (NASDAQ:PTLA)
Threshold Pharmas (NASDAQ:THLD)/Merck KGaA (Xetra:MRK)
ZS Pharma

Miraclins (TSX-V:VOM)
NeuroPhage Pharma
Oasma Pharma (SSE:OASM A)
Rui’Yi
Scilex Pharma
scPharmas
Transgene (Euronext:TNG)
Verona Pharma (LSE:VRP)
Vigilant Bio

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Ariosa Diagnostics
Cellectis (Euronext:ALCLS)
Karyopharm Therap (NASDAQ:KPTI)
Lorus Therap (TSX:JOR; Pink:LRUSF)
Mapi-Pharma
PledPharma (SSE:PLED)
Syndax Pharma

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Adamas Pharma
Corium Intl

Other Financial News (Page B35)

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Akebia (NASDAQ:AKBA)
Dyax (NASDAQ:DYAX)
Ipsen (Euronext:IPN; Pink:IPSEY)
MediWound (NASDAQ:MDWD)
Versartis (NASDAQ:VSAR)

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Advaxis (NASDAQ:ADXS)
Antibe Therap (TSX-V:ATE)
Applied Genetic Tech (NASDAQ:AGTC)
Arch Biopartners (CNSX:ACH)
CAP-CMV
Endocyte (NASDAQ:ECYT)
Generex Bio (OTCBB:GNBT)
Horizon (LSE:HZD)
KinDex Pharma
Kolttan Pharma

Miraculins (TSX-V:VOM)
NeuroPhage Pharma
Oasma Pharma (SSE:OASM A)
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MediWound (NASDAQ:MDWD)
Versartis (NASDAQ:VSAR)
intangible assets and other related programs. All rights revert back to Biotie, which said a Phase III trial of the selective adenosine A2A receptor (ADORA2A) antagonist is expected to start in 1H15. Biotie said the write-off is the only financial implication of the termination. Biotie said it will consider other partners to assist in the development and commercialization of tozadenant. Biotie said it will give further guidance on any changes in the development timeline next quarter.

Under the February amendment to the deal, responsibility for Phase III testing transferred to Biotie from UCB, while UCB remained responsible for the manufacture and commercialization of the product (see BioCentury, Oct. 18, 2010 & March 4, 2013).

Biotie gained rights to the product through its acquisition of Synosia Therapeutics AG. Synosia had rights from Roche (SIX:ROG; OTCQX:RHHBY, Basel, Switzerland) (see BioCentury, Feb. 7, 2011).

**Cytovalle Inc.**, South San Francisco, Calif.

**NetScientific plc**, (LSE:NSCI), Cambridge, U.K.

**Thiel Foundation**, San Francisco, Calif.

Business: Other

Biotie IP commercialization firm NetScientific will purchase a convertible note for up to $250,000 in medical technology companies that receive awards from the Thiel Foundation’s Breakout Labs program. The Breakout Labs program awards up to $350,000 for very early stage companies. The partners plan to co-invest in four to six companies a year.

The first Breakout Labs recipient to receive a NetScientific investment is Cytovalle, which is developing a microfluidic platform to detect biophysical changes in white blood cells associated with early stages of sepsis. NetScientific identifies and invests in late-stage translational research from academic institutions worldwide, with a focus on the U.S. and U.K.

Recipients of Breakout Labs grants are required to pay a 3% royalty capped at three times the original amount, once the company has $100,000 in revenue. Additionally, the value of the award converts to equity and warrants when the company completes its next round of funding.

**Genable Technologies Ltd.**, Dublin, Ireland


Business: Gene/Cell therapy, Ophthalmic

Spark granted Genable exclusive, worldwide rights to patents covering manufacturing of adeno-associated virus (AAV) vectors to treat rhodopsin-linked retinitis pigmentosa (RP). Spark will be the exclusive manufacturer for Genable’s lead product, GT038, which is in preclinical testing to treat RP. Spark will provide development advice in the development of GT038. Spark will receive an upfront payment, payments for the manufacture and supply of GT038 and is eligible to receive milestones and royalties. GT038 has Orphan Drug designation in the U.S. to treat RP and in the EU to treat rhodopsin-linked RP. The product is an AAV vector encoding an RNAi targeting rhodopsin (Rho; Opn2) in combination with an AAV vector containing a Rho gene. Genable expects to start Phase I testing in 2016. The partners declined to disclose financial details.

Spark’s AAV2-hRPE65v2, an AAV serotype 2 vector encoding the retinal pigment epithelium-specific protein 65kDa (RPE65) gene, has completed enrollment in a Phase III trial in patients with Type 2 Leber’s congenital amaurosis (LCA2).

**Genentech Inc.**, South San Francisco, Calif.

**Xenon Pharmaceuticals Inc.**, Burnaby, B.C.

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

Business: Neurology

Xenon partnered with Roche’s Genentech unit to discover and validate novel targets and mechanisms to treat pain. The partners, which will both own resulting IP, will use Xenon’s Extreme Genetics discovery platform to focus on rare phenotypes in which patients have an inability to perceive pain or have non-precipitated spontaneous severe pain. Genentech received a time-limited, exclusive right of negotiation on a target-by-target basis to form joint drug discovery collaborations. Xenon declined to disclose further details. Genentech said it made an upfront payment, but declined to disclose further financial terms.

Xenon and Genentech partnered in December 2011 to discover and develop oral inhibitors of sodium channel subunit Nav1.7 (SCN9A) and companion diagnostics to treat pain. Xenon has received a $5 million milestone payment from Genentech triggered by the selection of a development-stage drug candidate and is eligible for an additional $621 million in milestones (see BioCentury, Jan. 16, 2012).

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

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

Business: Cancer

Genmab will receive a $22 million milestone payment from Johnson & Johnson’s Janssen Biotech Inc. unit under an August 2012 deal granting the unit exclusive, worldwide rights to daratumumab. The milestone, the second under the deal, was triggered by undisclosed progress in an ongoing Phase II trial in multiple myeloma (MM) patients who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are double refractory to a PI and an IMiD. The partners declined to disclose what specifically triggered the milestone. The human mAb against CD38 has breakthrough therapy designation and Fast Track designation in the U.S. for the indication. Under the deal, Genmab is eligible for up to $1 billion in milestones, plus tiered double-digit royalties (see BioCentury, Sept. 3, 2012; May 6, 2013 & Dec. 9, 2013).

Earlier this month, Genmab said Janssen Biotech would begin a Phase III trial of daratumumab next month to treat relapsed or refractory MM.

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

**MAB Discovery GmbH**, Neuried, Germany

Business: Antibodies

Genmab partnered with MAB Discovery to discover antibodies against multiple undisclosed targets selected by Genmab. MAB will generate the antibodies using its in vivo discovery platform, which relies on the natural immune response of rabbits followed by B cell cloning and high throughput screening to yield high-affinity mAbs. MAB also said it might use Genmab’s DuoBody and HexaBody platforms. The DuoBody technology creates human bispecific antibodies that bind to two different epitopes on the same or different disease targets, and the HexaBody technology increases the potency of antibodies. The companies are not disclosing financial terms.

**Guerbet S.A.** (Euronext:GBT), Villepinte, France

**Sirtex Medical Ltd.** (ASX:SRX), Sydney, Australia

Business: Cancer, Diagnostic

The companies partnered to develop Sirtex’s SIR-Spheres microspheres and Guerbet’s Lipiodol ethiodized oil to be used in combination or in sequence to treat inoperable primary and secondary liver cancers. The first project under the deal will comprise a series of clinical trials to evaluate the potential for synergism between the two therapies, and whether they can be combined or sequenced to deliver optimized tumor control. The partners could not be reached in time for publication.

SIR-Spheres comprise yttrium-90 microspheres used for selective See next page
internal radiation therapy (SIRT). The product is approved in the EU, U.S., Australia, New Zealand, Switzerland and Turkey to treat unresectable liver tumors. Lipiodol is approved in the U.S. for use during diagnostic radiological examinations or to prevent iodine deficiency disorders when iodization of salt or drinking water cannot be undertaken. The iodinated contrast agent obtained from poppy seed oil has Orphan Drug designation in the U.S. to manage patients with known hepatocellular carcinoma (HCC). The product is under FDA review to extend its indication to include selective hepatic intra-arterial use in computed tomography of the liver to visualize and localize lesions in adults with known HCC.

IntelliCell BioSciences Inc. (OTCQB:SVFC), New York, N.Y.
New York University, New York, N.Y.
Business: Neurology
IntelliCell partnered with Manuel Trujillo, chief psychiatrist at Amen Clinics in New York and clinical professor of psychiatry at NYU School of Medicine, to develop joint clinical study protocols to evaluate the use of IntelliCell’s autologous adipose-derived stromal vascular fraction cells to treat amyotrophic lateral sclerosis (ALS). The company said the joint protocols will be conducted under an IND. IntelliCell’s technology separates stromal vascular fraction to produce adipose-derived adult stem cells for use in tissue processing centers and doctor’s offices. IntelliCell said it is in the “infancy stage” of planning the trial and declined to provide a timeline.

Manchester Pharmaceuticals LLC, Fort Collins, Colo.
Retrophin Inc. (NASDAQ:RTRX), New York, N.Y.
Business: Cardiovascular, Gastrointestinal, Endocrine/Metabolic
Retrophin completed its acquisition of offshore rare disease company Manchester for $62.5 million, including $29.5 million up front, plus undisclosed royalties (see BioCentury, Feb. 17).

Myriad Genetics Inc. (NASDAQ:MYGN), Salt Lake City, Utah
Tesaro Inc. (NASDAQ:TSRO), Waltham, Mass.
Business: Pharmacogenetics
Tesaro will use Myriad’s Homologous Recombination Deficiency (HRD) test to identify tumor types that may respond to Tesaro’s niraparib. The oral poly(ADP-ribose) polymerase (PARP) inhibitor is in Phase III testing to treat breast and ovarian cancer. Myriad’s HRD test detects when a tumor has lost the ability to repair double-stranded DNA breaks resulting in increased susceptibility to DNA-damaging drugs. The partners declined to disclose details. Tesaro has exclusive, worldwide rights to niraparib from Merck & Co. Inc. (NYSE:MRK, Whitehouse Station, N.J.) (see BioCentury, June 11, 2012).

Under a June 2013 deal, Tesaro will use Myriad’s BRACAnalysis to select patients likely to respond to niraparib for enrollment in Phase III trials of the product. Myriad markets BRACAnalysis to assess a woman’s risk of developing breast or ovarian cancer based on detecting genetic mutations in the breast cancer 1 early onset (BRCA1) and BRCA2 genes (see BioCentury, June 11, 2012 & July 1, 2013).

Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Business: Infectious, Drug delivery
NanoBio granted Merck exclusive, worldwide rights to NanoBio’s nanoemulsion-based adjuvant technology for use in an intranasal respiratory syncytial virus (RSV) vaccine and non-exclusive, worldwide rights for use in an intranasal seasonal influenza and/or universal seasonal influenza vaccine. NanoBio will receive an upfront payment and is eligible to receive milestones and royalties.

NanoBio’s nanoemulsion-based technology can incorporate, deliver and adjuvant multiple antigen types. The partners declined to disclose financial details.

New York Genome Center (NYGC), New York, N.Y.
IBM Corp. (NYSE:IBM), Armonk, N.Y.
Business: Pharmacogenetics
IBM and the non-profit NYGC will jointly evaluate a prototype of IBM’s Watson cognitive system designed as a genomic research tool to help oncologists deliver personalized care initially for patients with glioblastoma. The prototype is expected to identify patterns in genome sequences, biomedical literature and drug databases to gain insights that will help clinicians treat patients. The information from Watson will be used by clinicians to consider a variety of treatment options that can be tailored to patients’ genetic mutations. The information will also help scientists understand data detailing gene sequence variations between normal and cancerous biopsies of brain tumors.

Pacgen Life Science Corp. (TSX-V:PBS), Vancouver, B.C.
General Biologicals Corp. (GreTai-E:4117), Hsinchu, Taiwan
Business: Genitourinary, Dermatology, Ophthalmic
The companies closed a deal under which Pacgen granted General Biologicals exclusive, worldwide rights to develop and commercialize products containing PAC-113 or related peptides to treat oral, vaginal, dermatological and ophthalmic conditions. The companies announced a preliminary deal in January. The deal excludes transitional skin mucous membrane areas of the mouth. Pacgen will receive $250,000 up front and minimum annual royalties of $50,000 independent from sales or development. Pacgen is also eligible for a $50,000 milestone payment each time General Biologicals receives a regulatory approval and royalties of 12% of net sales or sublicensing revenues. As of Feb. 17, General Biologicals owned about 9.6 million Pacgen shares, or about 20%, and General Biologicals Chairman Tsong Chin Lin owned about 10.7 million shares, or about 23% (see BioCentury, Feb. 3).

Pacgen has worldwide rights to PAC-113 under an amended March 2005 deal with Demegen Inc. (Pink:DBOT, Pittsburgh, Pa.). The product is an oral mouth-rinse formulation of a 12 amino-acid antimicrobial peptide derived from a naturally occurring histatin protein found in human saliva. The product completed Phase Ib testing (see BioCentury, March 28, 2005 & Feb. 6, 2012).

Rosetta Genomics Ltd. (NASDAQ:ROSG), Rehovot, Israel
Rabin Medical Center, Petah-Tikva, Israel
Business: Diagnostic
Rosetta and not-for-profit Rabin Medical Center partnered to develop a non-invasive microRNA-based assay to diagnose chronic allograft dysfunction in kidney transplant recipients. Rosetta will partially fund the two-year project and will receive exclusive, worldwide rights to technology resulting from the deal. In 2008, the parties partnered to develop miRNA-based diagnostics for oncology, gynecology and obstetrics. The partners could not be reached for details (see BioCentury, June 30, 2008).

Singulex Inc., Alameda, Calif.
Tecan AG (SIX:TECN), Mannedorf, Switzerland
Business: Diagnostic
The companies will co-develop the Sgx Clarity ultrasensitive immunoassay system for in vitro diagnostics. The system will combine Singulex’s single molecule counting technology with Tecan’s Freedom EVO liquid handling platform. Singulex will commercialize the automated bench-
SQI Diagnostics Inc. (TSX-V:SQD), Toronto, Ontario
Business: Pharmaceuticals
SQI expanded its deal to develop a custom multiplex test for a drug from an undisclosed pharma. Under the expansion, SQI will develop a 21-plex protein microarray for identifying immunogenic regions within the drug during clinical testing. In the first phase of the deal, SQI developed a series of multiplex antidrug antibody assays to detect immunogenic responses to the drug during preclinical testing. SQI declined to disclose details.

TapImmune Inc. (OTCBB:TPIV), Seattle, Wash.
Business: Cancer
TapImmune signed an exclusive option agreement with Mayo for peptide epitopes targeting folate receptor 1 (FOLR1; FR-alpha) in breast and ovarian cancer. TapImmune said that a Phase I trial evaluating a multi-epitope FOLR1 peptide vaccine conducted by Mayo is ongoing. TapImmune declined to disclose details, and Mayo could not be reached. Mayo is also conducting a Phase I trial evaluating an HER2/neu peptide vaccine, a multi-epitope vaccine using epidermal growth factor receptor 2 (EGFR2; HER2; ErbB2; neu) class II antigens. TapImmune is sponsoring the trial and has an exclusive option to license the antigen technology at the end of Phase I testing (see BioCentury, March 10).

Upsher-Smith Laboratories Inc., Maple Grove, Minn.
Vertical Pharmaceuticals LLC, Sayreville, N.J.
Business: Endocrine/Metabolic
Vertical acquired Upsher-Smith’s rights to Divigel estradiol gel, probiotic supplement Provela and prenatal vitamin Nexa Plus. The companies did not disclose financial terms. Divigel, a 0.1% estradiol gel, is approved in the U.S. to treat moderate to severe hot flashes due to menopause. Upsher-Smith marketed Divigel in the U.S. under a 2007 deal with Orion Corp. (HSE:ORNAV; HSE:ORNBV, Espoo, Finland).
Vertical is the branded pharmaceuticals arm of Vertical/Trigen Holdings. In December, private equity firm Avista Capital Partners (New York, N.Y.) acquired an undisclosed controlling equity interest in Vertical/Trigen (see BioCentury, Jan. 6).

Vectura Group plc (LSE:VEC), Chippingham, U.K.
Business: Inflammation, Pulmonary, Drug delivery
Vectura will receive a $3 million milestone payment from the U.S. division of an undisclosed pharma under a 2011 deal granting the pharma rights to develop and commercialize VR315 in the U.S. VR315 is a combination of salmeterol, a long-acting adrenergic receptor beta 2 agonist (LABA), and fluticasone, an inhaled corticosteroid, that uses Vectura’s GyroHaler dry powder inhaler. The compound is being developed to treat asthma and chronic obstructive pulmonary disease (COPD). Vectura, which declined to disclose details, said it is eligible to receive an additional $29 million in milestones under the deal, plus royalties. Vectura’s GyroHaler has received FDA approval. Bunavail is a buprenorphine and naloxone polymer film formulated with BioDelivery’s BioErodible MucoAdhesive (BEMA) transmucosal delivery system.

Biohit Oyj (HSE:BIOBV), Helsinki, Finland
Business: Diagnostic
Biohit launched its Calprotectin test in Europe, the Middle East and Asia for early detection and monitoring of inflammatory bowel disease (IBD), such as Crohn’s disease and ulcerative colitis. The test measures fecal calprotectin levels and can differentiate between IBD and inflammatory bowel syndrome (IBS). Biohit could not be reached for details.

Cardiome Pharma Corp. (TSX:COM; NASDAQ:CRME), Vancouver, B.C.
Business: Cardiovascular
Cardiome’s Cardiome International A.G. subsidiary granted Vianex rights to commercialize IV Brinavess vernakalant in Greece. The renewable three-year deal includes specific annual commercial goals. Cardiome said financial terms are not disclosed, and the partners could not be reached for details in time for publication. The mixed ion channel blocker Brinavess is not approved in Greece. The test measures fibrinogen levels and can differentiate between IBD and inflammatory bowel syndrome (IBS). Biohit could not be reached for details.

CSL Ltd. (ASX:CSL), Melbourne, Australia
Business: Hematology
CSL’s CSL Behring subsidiary launched the My Access cost share program, which covers up to $12,000 in annual out-of-pocket costs of
Sales & Marketing, from previous page

a CSL Behring therapy for hemophilia A or von Willebrand disease (vWD) for patients in the U.S. who have private insurance. The company said the patient’s private insurance must cover their CSL Behring therapy. My Access will be available through CSL Behring’s My Source program, which offers information, financial support programs and community connections for the bleeding disorders community.

CSL Behring markets Humate-P, a lyophilized concentrate of anti-hemophilic factor and von Willebrand factor (vWF) complex, and Stimate desmopressin, a synthetic analogue of vasopressin, in the U.S. for hemophilia A and vWD. The company also markets recombinant Factor VIII (rFVIII) products Helixate FS and Monoclate-P in the U.S. for hemophilia A.

GiaxsoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
U.S. Centers for Medicare & Medicaid Services (CMS), Baltimore, Md.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.
Business: Pharmaceuticals

The pharma said they are not redeeming co-pay coupons for patients enrolled in plans on the Affordable Care Act’s health exchanges. In separate statements, both companies cited existing HHS guidance as motivating the decisions and emphasized non-acceptance of coupons “currently” or “at this time,” signaling the policies could change with clarity from HHS.

Late last year, CMS and HHS created confusion around the issue of third-party payments for plans through the exchanges, with an HHS letter indicating coupons would be allowed followed by a statement in which CMS said it “discourages” them. In February, CMS said in a memo that plans on ACA exchanges are “encouraged” to accept payments from some third parties but did not address co-pay assistance provided by drug companies (see BioCentury, Nov. 11, 2013).

Amgen Inc. (NASDAQ:AMGN, Thousand Oaks, Calif.), Bristol-Myers Squibb Co. (NYSE:MY, New York, N.Y.), Eli Lilly and Co. (NYSE:LLY, Indianapolis, Ind.), Gilead Sciences Inc. (NASDAQ:GILD, Foster City, Calif.) and Johnson & Johnson (NYSE:JNJ, New Brunswick, N.J.) all said they will still offer co-pay assistance for patients on exchange plans. The Pharmaceutical Research and Manufacturers of America (PhRMA) could not be reached for comment on its position; could not be reached for comment.

Gruppo Ferrer International S.A., Barcelona, Spain
Medimetriks Pharmaceuticals Inc., Fairfield, N.J.
Business: Infectious

Ferrer granted Medimetriks exclusive commercialization rights to ozenoxacin 1% formulation in the U.S., including Puerto Rico and the U.S. Virgin Islands. Ferrer is eligible for undisclosed milestones and royalties in the territories. Ozenoxacin 1% has completed a Phase III trial in adult and pediatric patients with impetigo. Next quarter, Ferrer plans to start a second Phase III trial in the indication. The company expects to complete the trial in 2Q15. Ferrer has exclusive, worldwide rights to the non-fluorinated quinolone antibacterial that inhibits DNA gyrase and topoisomerase IV outside of China, Japan, Korea and Taiwan from Toyama Chemical Co. Ltd. (Tokyo, Japan).

Medline Industries Inc., Mundelein, Ill.
Business: Dermatology

Medline launched Revitalon amniotic membrane allografts in the U.S. for wound covering. The Musculoskeletal Transplant Foundation (Edison, N.J.) procures and processes the tissue used in Revitalon. Medline uses undisclosed processing technology from Liventa Biotechnology (West Conshohocken, Pa.).

Merz GmbH & Co. KGaA, Frankfurt, Germany
Business: Neurology

Merz’s U.S. subsidiary Merz Pharmaceuticals LLC will launch on April 1 the My Merz Select physician loyalty program for its aesthetic products. Merz markets OTC aesthetic products and prescription aesthetic products, including Xeomin incobotulinumtoxinA. The product is approved in the U.S. as a temporary improvement in the appearance of moderate to severe glabellar lines (frown lines between the eyebrows) and to treat cervical dystonia or blepharospasm in patients previously treated with Botox onabotulinumtoxinA. Allergan Inc. (NYSE:AGN, Irvine, Calif.) markets Botox.

NovaMedica LLC, Moscow, Russia
SIFI S.p.A., Aci S. Antonio, Italy
Business: Ophthalmic

SIFI granted NovaMedica exclusive rights to commercialize eight ophthalmic products in the Commonwealth of Independent States (CIS). The products include Eystiel sodium hyaluronate and Lacriscif to treat dry eye; antibiotics Colbicin, Nettavis netilmicina and Nettacin netilmicina to treat external eye infections; Prenacid, a corticosteroid to treat inflammation and allergies; Octilia to treat irritation, reddening and pruritus; and vasoprotective agent Mirtiline Forte. NovaMedica plans to begin selling the products later this year. The products are approved in Russia and the EU. NovaMedica declined to disclose details. SIFI could not be reached for comment.

Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
Business: Gastrointestinal

The pharma partnered to co-promote Takeda’s TAK-438 in Japan. Otsuka will pay Takeda ¥20 billion ($196 million) up front and an undisclosed milestone upon Japanese approval of TAK-438, which is under review in Japan to treat acid-related diseases. Otsuka will receive an undisclosed percentage of sales from Takeda. The Japanese Phase III program for the small molecule potassium competitive acid blocker included gastric ulcer, duodenal ulcer and erosive esophagitis. The pharma could not be reached for details.

Actavis plc (NYSE:ACT), Dublin, Ireland
Hisamitsu Pharmaceutical Co. Inc. (Tokyo:4530), Tosu, Japan
Business: Neurology

Hisamitsu’s Noven Pharmaceuticals Inc. subsidiary granted Actavis a non-exclusive, royalty-bearing license to market a generic version of Daytrana methylphenidate transdermal system for ADHD beginning on Sept. 1, 2015. The deal settles all outstanding patent litigation related to Actavis’ generic Daytrana. Actavis said additional details of the settlement are not disclosed. Hisamitsu reported ¥4.6 billion ($43.3 million) in Daytrana sales for first nine months of fiscal year ending Feb. 28, 2014. Noven reacquired Daytrana from Shire plc (LSE:SHP, NASDAQ:SHPG, Dublin, Ireland) in 2010 (see BioCentury, Oct. 11, 2010).

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

AstraZeneca launched its Open Innovation website, which lists programs available for partnering and invites proposals for further.
development. At launch, the website provides preclinical and clinical data and potential disease areas for 46 compounds, including discontinued programs and new compounds remaining in the pharma’s pipeline for which AZ is seeking partners for new indications.

The website also includes a route for interested parties to submit proposals to the pharma for grants of up to $100,000 for target validation partnerships; and an “R&D Challenges” section where the pharma plans to crowd-source solutions to problems. In May, AZ plans to post more information about a discovery program that will provide screening assays and other assistance to external investigators while allowing the external partner to retain IP to discovered compounds. AstraZeneca could not be reached for details.

The website launch is the latest step in the pharma’s open innovation program. Last year, AZ partnered with Roche (SIX:ROG; OTCQX:RHHBY, Basel, Switzerland) to share data on optimizing drug design. And in 2011, AZ partnered with the U.K.’s Medical Research Council to provide academic researchers access to 22 of the pharma’s compounds free of charge (see BioCentury, Dec. 12, 2011 & July 1, 2013).

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

Business: Pharmaceuticals, Biosimilars

Baxter said it will split its medical products and biopharmaceuticals businesses into two public companies. The pharma said the businesses operate in distinct markets and have different “growth prospects, investment requirements and risk profiles.” Baxter shareholders will receive a tax-free distribution of stock in the new pharma at a to-be-determined ratio. The split is expected to be completed by mid-2015.

The biopharmaceuticals business, which will be named later, will house Baxter’s recombinant and plasma-based proteins to treat hemophilia, immune deficiencies, alpha 1-antitrypsin (AAT; SERPINA1) deficiency, burns, shock and other chronic and acute blood-related conditions, including myelofibrosis. The newco also will house Baxter’s biosimilar pipeline; the pharma is separately partnered with Momenta Pharmaceuticals Inc. (NASDAQ:MNTA, Cambridge, Mass.) and Coherus BioSciences Inc. (Redwood City, Calif.) to develop biosimilars. The biopharmaceuticals business had 2013 revenues of $5.8 billion. Ludwig Hantson, corporate VP and president of Baxter’s BioScience business, will be CEO. Wayne Hockmeyer, a Baxter director, will be chairman (see BioCentury, Jan. 2, 2012 & Sept. 9, 2013).

The medical products business will retain Baxter’s name and will house products that include the pharma’s IV solutions and nutritional therapies, drug delivery systems, inhalation anesthetics and hospital-based biosurgery products. The business had 2013 revenues of $9.4 billion. Baxter CEO and Chairman Robert Parkinson will retain his roles. Both companies will be headquartered in northern Illinois.

Baxter also said it is exploring options to divest its Vero cell culture technology, including its influenza treatments, and its Lyme disease program.

Emergent BioSolutions Inc. (NYSE: EBS), Rockville, Md.
Mapp Biopharmaceutical Inc., San Diego, Calif.
Zalgen Labs LLC, Germantown, Md.
Ben-Gurion University of the Negev, Beer-Sheva, Israel
National Institutes of Health, Bethesda, Md.
Public Health Agency of Canada, Winnipeg, Manitoba
The Scripps Research Institute, La Jolla, Calif.
Uganda Virus Research Institute, Entebbe, Uganda
University of Texas Medical Branch, Galveston, Texas
University of Wisconsin, Madison, Wis.
U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Md.
Yeshiva University, New York, N.Y.

Business: Infectious

NIH’s National Institute of Allergy and Infectious Disease (NIAID) awarded a consortium led by Scripps a five-year grant worth up to $28 million to develop immunotherapies for filoviruses and arenaviruses that cause severe hemorrhagic fever, including Ebola, Marburg, Sudan and Lassa viruses. The consortium has gathered about 315 mAbs against the filoviruses and 100 mAbs against the arenaviruses. The consortium’s goal is to submit one or more INDs for mAb-based immunotherapies against these viruses by year five. Scripps said Mapp is performing industrial-level expression of antibodies, Zalgen is helping to generate antibodies against the arenaviruses, and Cangene Corp., which Emergent acquired earlier this year, is donating a few antibodies against the Ebola virus (see BioCentury, March 3).

Gilead Sciences Inc. (NASDAQ: GILD), Foster City, Calif.
Idenix Pharmaceuticals Inc. (NASDAQ: IDIX), Cambridge, Mass.

Business: Infectious

Idenix said the Oslo, Norway District Court ruled that Idenix’s Norwegian Patent No. 330,755 is invalid and that Gilead’s Norwegian Patent No. 333,700 is valid. Both patents cover the use of 2’-methyl, 2’-fluoro nucleoside compounds to treat HCV infection. In September 2012, Gilead filed the patent invalidity case claiming that Idenix’s patent is invalid and Idenix filed with a counterclaim challenging the validity of Gilead’s patent. Idenix said it plans to appeal the ruling.

Earlier this month, Idenix said it filed suit against Gilead in France, Germany and the U.K. alleging Gilead infringes Idenix’s European Patent No. EP 1,523,489 related to the use of 2’-methyl, 2’-fluoro nucleoside compounds to treat HCV infection. Idenix is seeking remedies related to sales of Gilead’s HCV drug Sovaldi sofosbuvir (see BioCentury, March 24).

In December, Idenix said the U.S. Patent and Trade Office declared a patent interference between Idenix’s U.S. Patent No. 7,608,600 and Gilead’s U.S. Patent application 11/854,218. The patent and patent application are both related to the use of 2’-methyl, 2’-fluoro nucleoside compounds for HCV infection. Idenix said the PTO declared Idenix as the senior party in the interference, which places the burden of proof on Gilead to demonstrate that it invented the technology before Idenix. Earlier in December, Idenix filed two patent infringement suits against Gilead relating to Sovaldi. In one of the suits, filed in the U.S. District Court for the District of Delaware, Idenix alleges that Sovaldi infringes the ‘600 patent and that Gilead’s U.S. Patent No. 8,415,322 covering Sovaldi is invalid as it interferes with the ‘600 patent (see BioCentury, Dec. 9, 2013 & Dec. 23, 2013).

The European Commission approved the nucleotide analog HCV NS5B polymerase inhibitor to treat chronic HCV infection in January, and Health Canada approved the drug in December.

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
European Bioinformatics Institute of the European Molecular Biology Laboratory (EMBL-EBI), Hinxton, U.K.
Wellcome Trust Sanger Institute, Hinxton, U.K.

Business: Functional genomics

GlaxoSmithKline partnered with the two European research institutes to form the Centre for Therapeutic Target Validation (C TT V), which will use genome sequencing and big data tools to research drug targets. The new center will have up to 50 researchers from the three partners. GSK said the parties are working to determine an initial set of projects for the center, which is expected to be fully functional next half. The parties are each providing resources, skills and platform technologies. GSK also provided an undisclosed “multi-million pound
Other News, from previous page

contribution.” Sequence data and other information gathered at the center will be publicly shared. CTTV will be based at the Wellcome Trust Genome Campus near Cambridge, U.K.

IntegraGen S.A. (Euronext:ALINT), Evry, France
Gustave Roussy Institute, Villejuif, France
Business: Pharmacogenetics, Genomics
Next quarter, IntegraGen will install and operate on behalf of the institute a high throughput, large-scale clinical sequencing unit at the institution’s molecular medicine building. The unit will be used for whole exome and RNA sequencing and will be used within the framework of personalized medicine cancer programs developed by the institute. IntegraGen will use the NextSeq 500 System from Illumina Inc. (NASDAQ:ILMN, San Diego, Calif.) in the unit. IntegraGen said that it will own, finance and operate the unit and Gustave will pay on a fee-for-service basis. Any IP generated at the unit through the personalized medicine programs will be owned by Gustave. The parties will share IP generated from an ongoing research-based partnership. IntegraGen declined to disclose financial details.

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Business: Neurology
The Arkansas Supreme Court reversed and remanded a 2012 lower court ruling, which fined Johnson & Johnson $1.2 billion for violating state fraud statutes through promotional practices of its antipsychotic Risperdal risperidone. The Supreme Court found that the Pulaski County Circuit Court incorrectly applied state law that governs healthcare facilities, which J&J is “indisputably not.”

Last year, the pharma agreed to pay about $2 billion to the federal government and state Medicaid programs and also pled guilty to one count of misdemeanor misbranding to settle federal and state investigations regarding the conduct of the company’s directors (see BioCentury, Oct. 5, 2009).

Sequenom Inc. (NASDAQ:SQNM), San Diego, Calif.
Business: Diagnostic
Sequenom said it resolved litigation between the company and former CFO Paul Hawran. The company declined to disclose terms of the resolution. Hawran filed the case, Hawran v. Hixson et al., in 2010 in the Superior Court of California for the County of San Diego. He alleged that Sequenom defamed him, invaded his privacy and conducted unfair business practices. Hawran served as CFO during 2007-09. In September 2009, Sequenom said it “obtained the resignation” of CFO Paul Hawran and terminated five employees after an independent investigation found the diagnostic company failed to put in place adequate protocols and controls for its Trisomy 21 program, resulting in “inadequately substantiated claims, inconsistencies and errors.” Hawran alleged that he was asked to resign after raising concerns regarding the conduct of the company’s directors (see BioCentury, July 18, 2011).

Zyomyx Inc., Fremont, Calif.
Business: Diagnostic
Zyomyx received $7.5 million from the World Health Organization’s international drug purchase facility, UNITAID, to commercialize Zyomyx’s MyT4 point-of-care CD4 test. The test identifies the concentration of CD4 T lymphocytes in patients with HIV/AIDS infection. The test has CE Mark approval and is available worldwide but does not have FDA clearance. Zyomyx said the grant will go towards the test’s initial commercialization in Ethiopia, Kenya, Malawi, Mozambique, Uganda, Tanzania, Zimbabwe and Southern Africa. Mylan Inc. (NASDAQ:MYL, Canonsburg, Pa.) has exclusive rights to distribute the test in Africa, Asia (excluding Japan and South Korea), Central Eastern Europe, the Commonwealth of Independent States (CIS), South and Central America and the Caribbean Islands (see BioCentury, July 15, 2013 & Jan. 20, 2014).

MANAGEMENT TRACKS

Boards of Directors

Arno Therapeutics Inc. (OTCQB:ARNI), Flemington, N.J.
Business: Cancer
Appointed: Randy Thurman, a director, as vice chairman

Exact Sciences Corp. (NASDAQ:EXAS), Madison, Wis.
Business: Diagnostic
Appointed: Kevin Conroy, president, CEO and a director, as chairman; he succeeds James Connelly, who resigned for personal reasons. See next page
Management Tracks, from previous page

Akers Biosciences Inc. (NASDAQ:AKER; LSE:AKR), Thorofare, N.J.
Business: Cardiovascular
Hired: Sara Bonstein as SVP and CFO; she replaces Mark Rosenblum as CFO, who departed

Advaxis Inc. (NASDAQ:ADXS), Princeton, N.J.
Business: Cancer
Hired: Sara Bonstein as SVP and CFO; she replaces Mark Rosenblum as CFO, who departed

AcelRx Pharmaceuticals Inc. (NASDAQ:ACRX), Redwood City, Calif.
Business: Neurology, Drug delivery
Hired: Timothy Morris as CFO, formerly SVP of finance and global corporate development and CFO of Vivus Inc.; he succeeds Jim Welch, who departed

Akser Biosciences Inc. (NASDAQ:AKER; LSE:AKR), Thorofare, N.J.
Business: Diagnostic, Supply/Service
Hired: Edwin Hendrick as EVP of sales and marketing, formerly EVP of sales and marketing at Plus Diagnostics

Business: Cardiovascular
Hired: Sam Teichman as CMO and a director

Calico, San Francisco, Calif.
Business: Other
Transitioned: Cynthia Kenyon to VP of aging research from part-time scientific advisor, formerly a professor at the University of California, San Francisco

Calithera Biosciences Inc., South San Francisco, Calif.
Business: Cancer
Hired: William Waddill as SVP and CFO, effective April 1, formerly SVP and CFO of OncoMed Pharmaceuticals Inc.

CAP-CMV GmbH, Cologne, Germany
Business: Infectious
Hired: Albrecht Laeufer as CEO, formerly CEO of Vakzine Projekt Management GmbH; he replaces Wolfgang Kintzel, who becomes a director

ChemoCentryx Inc. (NASDAQ:CCXI), Mountain View, Calif.
Business: Autoimmune, Inflammation, Cancer
Hired: Anne-Marie Duliege as EVP of corporate development and head of immuno-oncology, a newly created position, formerly head of research and CMO of Affymax Inc.

Discovery Laboratories Inc. (NASDAQ:DSCO), Warrington, Pa.
Business: Pulmonary
Transitioned: John Tattory to SVP and CFO from VP of finance

Immunocore Ltd., Abingdon, U.K.
Business: Cancer, Endocrine/Metabolic, Infectious
Departing: James Noble as CEO, while remaining a director, to become full-time CEO of Adaptimmune Ltd.; he will be replaced as acting CEO by Executive Chairman Jonathan Knowles

Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Business: Infectious
Hired: Robert Davis as CFO, effective April 23, currently VP and president of the medical products business at Baxter International Inc.; Davis will succeed Peter Kellogg, who will depart on May 16

Merck KGaA (Xetra:MRK), Darmstadt, Germany
Business: Pharmaceuticals, Other
Departing: Annalisa Jenkins as EVP and head of global R&D at Merck’s Merck Serono S.A. biopharmaceutical division; Belen Garijo, president and CEO of Merck Serono, will be in charge of R&D in the interim Promoted: Udit Batra to president and CEO of Merck’s EMD Millipore division, effective May 15, from president and CEO of the Merck’s consumer health division; he succeeds Robert Yates, who is departing; Batra will be succeeded as president and CEO of the consumer health division by Uta Kemmerich-Keil, currently CEO of Merck’s Alleghoparma allergy business; Kemmerich-Keil will be succeeded by Marco Linari

miRagen Therapeutics Inc., Boulder, Colo.
Business: Cardiovascular
Hired: David Rodman as EVP of R&D, formerly VP of clinical development at Vertex Pharmaceuticals Inc.

NPS Pharmaceuticals Inc. (NASDAQ:NPSP), Bedminster, N.J.
Business: Endocrine/Metabolic, Musculoskeletal, Gastrointestinal
Hired: Paul Firuta as president of U.S. commercial operations, formerly VP and general manager of the Americas at ViroPharma Inc., which Shire plc acquired Promoted: Eric Pauwels to president of NPS’ NPS Pharma International, a newly created position, from SVP and chief commercial officer

Osiris Therapeutics Inc. (NASDAQ:OSIR), Columbia, Md.
Business: Cancer, Cardiovascular, Musculoskeletal
Hired: Theresa Dixon as general manager of market access and reimbursement, formerly VP of government affairs and health economics at Advanced BioHealing Inc., which Shire plc acquired

Pixium-Vision S.A., Paris, France
Business: Ophthalmic
Hired: Khalid Ishaque as CEO and a director, formerly general manager of the neuromodulation international business of Boston Scientific Corp.

Renovo Group plc (LSE:RNVO), Manchester, U.K.
Business: Dermatology
**Regulatory**

**Aerocrine AB** (SSE:AERO), Solna, Sweden

Products: Niox Mino, Niox Vero
Business: Diagnostic

Aerocrine said that in final guidance to be published in April the U.K.'s NICE is recommending the use of Niox Mino and Niox Vero to improve diagnosis and management of eosinophilic asthma. The tests are recommended for use in subjects who, after initial clinical examination, are considered to have an intermediate probability of having asthma and when fractional exhaled nitric oxide (FeNO) testing is intended as part of the diagnosis. NICE issued preliminary guidelines recommending the products last year (see *BioCentury*, Nov. 18, 2013).

Niox Mino and Niox Vero are handheld point-of-care-devices, which measure FeNO as an assessment of airway inflammation in patients with asthma. Aerocrine markets Niox Vero, which is battery powered with an extended operational life and is intended to replace Niox Mino.

**Alimera Sciences Inc.** (NASDAQ:ALIM), Alpharetta, Ga., pSivida Corp. (NASDAQ:PSDV; ASX:PVA), Watertown, Mass.

Product: Iluvien fluocinolone acetonide intravitreal implant (formerly Medidur FA)
Business: Ophthalmic


**Alkerne Inc.** (NASDAQ:ALKS), Dublin, Ireland

Zogenix Inc. (NASDAQ:ZGNX), San Diego, Calif.

Product: Hydrocodone bitartrate (Zohydro ER) (ZX002)

Business: Neurology

Massachusetts Gov. Deval Patrick declared opiate addiction a public health emergency and directed state authorities to immediately prohibit the prescription or sale of Zogenix's pain drug, Zohydro ER hydrocodone bitartrate. Zohydro is an oral, non-abuse-deterrent, extended-release (ER) formulation of hydrocodone approved to manage chronic pain severe enough to require a continuous, around-the-clock opioid analgesic when alternatives are inadequate. Patrick said the ban would last until FDA approves an abuse deterrent formulation. Zogenix said the ban “unfairly restricts patient access” and noted that most other opioids on the market are “both equal to or more potent than Zohydro ER” and available in higher strengths. Zogenix launched Zohydro in select pharmacies earlier this month.

Zogenix has been under fire for Zohydro at the federal level from legislators as well as patient groups, addiction centers and state attorneys general, who have called on FDA Commissioner Margaret Hamburg to reconsider the agency’s approval of Zohydro or to set a rigorous timeline for the product to be reformulated to be abuse deterrent (see *BioCentury*, March 17). Last year, Zogenix partnered with Altus Formulation Inc. (Montreal, Quebec) to develop abuse-deterrent formulations of Zohydro. The company said it expects to launch abuse-deterrent formulations in 2016 (see *BioCentury*, Nov. 11, 2013).


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

**NPS Pharmaceuticals Inc.** (NASDAQ:NPSP), Bedminster, N.J.

**Kyowa Hakko Kirin Co. Ltd.** (Tokyo:4151), Tokyo, Japan

Product: Regpara cinacalcet (Sensipar, Mimpara - EU) (KRN1493, AMG 073)

Business: Endocrine/Metabolic

Kyowa submitted a regulatory application to Japan’s Ministry of Health, Labor and Welfare to enable the stage 2 trial of Regpara cinacalcet in Japan patients with type 1 diabetes and hyperparathyroidism. The drug is not approved in Japan.

**Management Tracks, from previous page**

Hired: Brian Cole as CEO and a director, effective May 1, formerly chief executive and managing director of Capital One U.K. plc

**Tobira Therapeutics Inc.** , San Francisco, Calif.

Business: Infectious

Hired: Chairman Laurent Fischer as CEO, formerly chairman and CEO of Jennerex Biotherapeutics Inc., which SillaJen Inc. acquired; he replaces Andrew Hindman, who resigned; and Christopher Peetz as CFO, formerly VP of finance and corporate development at Jennerex; he replaces Carolyn Loewy, who resigned

**Tocagen Inc.** , San Diego, Calif.

Business: Cancer, Gene/Cell therapy

Hired: Jamey Skillings as SVP and CMO, formerly VP of global medical affairs for oncology at Pfizer Inc.
Health, Labor and Welfare (MHLW) for the 12.5 mg tablet of Regpara cinacalcet. The 25 and 75 mg tablets of Regpara are approved to treat hypercalcemia in patients with parathyroid cancer and hypercalcemia in patients with primary hyperparathyroidism (HPT) who are unable to undergo parathyroidectomy or who experience recurrent primary HPT and to treat secondary HPT in patients who are undergoing regular dialysis. The tablets have been marketed in Japan since January 2008.

The second-generation calcimimetic is also marketed as Mimpara in the EU. Amgen markets the product as Sensipar in the U.S. for the indications and also to treat adults for secondary HPT in chronic kidney disease (CKD) patients on dialysis, hypercalcemia in adults with parathyroid cancer and severe hypercalcemia in adults with primary HPT who are unable to undergo parathyroidectomy. In 1995, NPS granted Kyowa exclusive rights to develop and commercialize cinacalcet in China, Japan, North and South Korea and Taiwan. In 1996, NPS granted Amgen exclusive, worldwide rights outside the Asian territories to the product (see BioCentury, Jan. 2, 1996).

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

**Product:** Forxiga dapagliflozin (Farxiga)

**Business:** Endocrine/Metabolic

Japan’s Ministry of Health, Labor and Welfare (MHLW) approved an NDA for AstraZeneca’s Forxiga dapagliflozin to treat Type II diabetes. In December, AZ and Ono Pharmaceutical Co. Ltd. (Tokyo:4528, Osaka, Japan) partnered to co-promote the sodium-glucose cotransporter 2 (SGLT2) inhibitor in Japan. The product is approved in more than 40 countries, including the U.S., where it is approved as Farxiga, and those of the EU (see BioCentury, Jan. 13). In February, AZ completed the acquisition of the diabetes business it shared with Bristol-Myers Squibb Co. (NYSE:BMY, New York, N.Y.), including dapagliflozin (see BioCentury, Feb. 10). BMS submitted the NDA to MHLW in March 2013.

**Avanir Pharmaceuticals Inc.** (NASDAQ:AVNR), Aliso Viejo, Calif.

**OptiNose Inc.**, Yardley, Pa.

**Product:** Intranasal sumatriptan powder, OptiNose sumatriptan (AVP-825)

**Business:** Neurology

FDA accepted for review an NDA from Avanir for AVP-825 to treat acute migraine. The PDUFA date is Nov. 26. The company submitted the application under section 505(b)(2) pathway of the Food, Drug and Cosmetic Act, which allows sponsors to reference data on safety and efficacy from scientific literature or from previously approved products. The product is a low-dose sumatriptan powder delivered intranasally using OptiNose Breath Powered intranasal technology. Avanir has exclusive, North American rights to develop and commercialize AVP-825 from OptiNose (see BioCentury, July 15, 2013).

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

**Product:** Xofigo radium-223 (BAY88-8223) (formerly Alpharadin)

**Business:** Cancer

The U.K.’s NICE issued a preliminary appraisal recommending against Bayer’s Xofigo radium-223 dichloride to treat adults with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastases — its approved indication in the EU. NICE said Bayer did not provide data comparing Xofigo to the appropriate treatments — docetaxel as a first-line treatment of CRPC and Zytiga abiraterone as second-line treatment. Bayer submitted data from the Phase III ALSYMPCA trial, which compared Xofigo plus best supportive care (BSC) vs. BSC alone; and the Phase II BC1-02 trial, which compared Xofigo with placebo.

Additionally, NICE said that even with an undisclosed discount under a patient access scheme, the incremental cost-effectiveness ratio (ICER) for Xofigo compared with BSC was £57,400 ($94,676) per quality-adjusted life year (QALY) gained. Comments are due April 11.


**Biogen Idec Inc.** (NASDAQ:BIIB), Weston, Mass.

**Genentech Inc.,** South San Francisco, Calif.

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

**Product:** MabThera rituximab (Rituxan) (R105, RG105)

**Business:** Inflammation

The U.K.’s NICE issued final guidance recommending MabThera rituximab from Roche in combination with glucocorticoids to induce remission in adults with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, also known as severely active granulomatosis with polyangiitis and microscopic polyangiitis. NICE only recommends MabThera if further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose; if cyclophosphamide is not suitable; if patients want children and cyclophosphamide might affect their fertility; if the disease has stayed active or got worse after a 3-6 month course of cyclophosphamide; or if the person has had urethral epithelial malignancy. The guidance is in line with a final appraisal determination issued in January (see BioCentury, Oct. 21, 2013). Roche did not submit a patient access scheme.

The chimeric mAb against CD20 antigen is approved in the EU for the indication and to treat non-Hodgkin’s lymphoma (NHL), chronic lymphocytic leukemia (CLL), diffuse large B cell lymphoma (DLBCL) and rheumatoid arthritis (RA). Biogen Idec and Roche’s Genentech unit co-market rituximab as Rituxan in the U.S., while Roche markets it as MabThera elsewhere. In Japan, rituximab is co-marketed as Rituxan by Chugai Pharmaceutical Co. Ltd. (Tokyo:4519, Tokyo, Japan), which is majority owned by Roche, and Zenyaku Kogyo Co. Ltd. (Tokyo, Japan).

**Biogen Idec Inc.** (NASDAQ:BIIB), Weston, Mass.

**Swedish Orphan Biovitrum AB** (SSE:SOBI), Stockholm, Sweden

**Product:** Alprolix rFIXFc, LongActing rFactor IX

**Business:** Hematology

FDA approved a BLA from Biogen Idec for Alprolix rFIXFc to control and prevent bleeding episodes, manage bleeding during surgical procedures and as prophylaxis in hemophilia B patients. Biogen Idec said it plans to launch Alprolix in the U.S. in early May. The company has not yet set a price for the product, a recombinant fusion protein consisting of human coagulation Factor IX attached to the Fc domain of human IgG1. Biogen Idec and partner Swedish Orphan said Alprolix is the world’s first approved long-acting hemophilia B therapy. The FDA approval came about a week after Health Canada approved Alprolix (see BioCentury, March 24).

Alprolix is under review in Australia and Japan. The product has Orphan Drug status in the U.S. and Orphan Drug designation in the EU for hemophilia B.

Swedish Orphan and Biogen Idec are partnered for Alprolix under an amended 2006 deal. The original deal was between Biovitrum AB and Syntoinix Pharmaceuticals Inc., which Biogen Idec acquired in 2007. Biovitrum acquired Swedish Orphan International AB in 2009 and

**BTG plc** (LSE:BTG), London, U.K.
**Sanofi** (Euronext:SAN; NYSE:SNY), Paris, France
Product: Lemtrada alemtuzumab (MabCampath, Campath)  
Business: Autoimmune  
Brazil’s Agencia Nacional de Vigilância Sanitária (ANVISA) approved Lemtrada alemtuzumab from Sanofi’s Genzyme Corp. unit to treat patients with relapsing forms of multiple sclerosis to slow or reverse the accumulation of physical disability and reduce the frequency of clinical exacerbations. The humanized mAb against CD52 is approved in Mexico, Canada, Australia and the EU. In December, Genzyme received a complete response letter from FDA for Lemtrada to treat relapsing MS. The product has Fast Track designation in the U.S. (see BioCentury, Jan. 6).

Chugai Pharmaceutical Co. Ltd.  
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Product: Serelaxin (RLX030) (formerly ConXn)  
Business: Cardiovascular  
Novartis has breakthrough therapy designation for serelaxin on the basis of the mortality benefit in the RELAX-AHF trial. The company believes that the improvement in VAS was driven by deterioration in heart failure in the placebo group and not the change in dyspnea. Moreover, the panel noted that investigators were not required to document the reason for worsening heart failure, and in many instances, the events appeared too mild and were easily treated with small increases in IV diuretics.

**TechnoPharm** from Stiefel Laboratories Inc. GlaxoSmithKline acquired Stiefel in 2009.  
**Endo International plc** (NASDAQ:ENDP; TSX:ENL), Dublin, Ireland
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.
Product: Latuda lurasidone (formerly ConXn)  
Business: Neurology  
Endo’s Sunovion Pharmaceuticals Inc. subsidiary markets Latuda in the U.S. and Canada to treat schizophrenia. Takeda markets it in Switzerland. The product is under review in Taiwan and in Phase III testing in Japan and in China.

**Chugai Pharmaceutical Co. Ltd.** (Tokyo:4519), Tokyo, Japan  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Product: Pegasys peginterferon alfa-2a (RG442)  
Business: Infectious  
EMA’s CHMP issued a positive opinion recommending expanding the label of Roche’s Pegasys peginterferon alfa-2a to include its use in combination with other drugs to treat chronic HCV infection in patients with compensated liver disease. The product is already approved to treat HCV infection in adults with compensated cirrhosis and/or who are co-infected with HIV. The pegylated recombinant interferon alfa-2a is also approved to treat chronic HCV infection in treatment-naive pediatric patients ages ≥2 years who are positive for serum HCV-RNA and chronic HBV infection in adults who have compensated liver disease and evidence of viral replication, increased alanine transaminase and liver inflammation and/or fibrosis. Chugai, which is majority owned by Roche, markets Pegasys in Japan.

**Daiichi Sankyo Co. Ltd.** (Tokyo:4568), Tokyo, Japan  
**Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind.
Product: Efient prasugrel (Effient)  
Business: Cardiovascular  
Japan’s Ministry of Health, Labor and Welfare (MHLW) approved an NDA from Daiichi Sankyo for Efient prasugrel to treat patients with ischemic heart disease undergoing percutaneous coronary intervention (PCI). Daiichi Sankyo and Eli Lilly market the purinergic receptor P2Y G protein-coupled 12 (P2RY12; P2Y12) antagonist as Efient to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) who are to be managed with PCI. The product is approved in more than 70 countries, including the U.S. and those in the EU.

**Dainippon Sumitomo Pharma Co. Ltd.** (Tokyo:4506), Osaka, Japan  
**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502), Osaka, Japan
Product: Latuda lurasidone (SM-13496)  
Business: Neurology  
The European Commission and Australia’s Therapeutic Goods Administration (TGA) separately approved Latuda lurasidone to treat schizophrenia in adults. Latuda is a small molecule antagonist of dopamine D2 receptor, serotonin (5-HT2A) and (5-HT7) receptors and adrenergic receptor alpha 2c (ADRA2C), and a partial agonist of serotonin (5-HT1A) receptor. Takeda has exclusive rights from Dai nippon to develop and commercialize the once-daily oral product for schizophrenia and bipolar disorder in the EU, Norway, Russia, Switzerland and Turkey (see BioCentury, May 16, 2011).

Dainippon’s Sunovion Pharmaceuticals Inc. subsidiary markets Latuda in the U.S. and Canada to treat schizophrenia. Takeda markets it in Switzerland. The product is under review in Taiwan and in Phase III testing in Japan and in China.

**Chembio Diagnostics Inc.** (NASDAQ:CEMI), Medford, N.Y.
Product: HIV 1/2 Stat-Pak Assay  
Business: Diagnostic  
Chembio said it received CE Mark approval for its HIV 1/2 Stat-Pak Assay for rapid, point-of-care detection of HIV. The company expects to launch the lateral flow rapid test that detects HIV antibodies in serum, plasma and venous or fingerstick whole blood specimens.

**BioCentury, April 6, 2009 & June 8, 2009).**

**Regulatory, from previous page**
Cologuard is under parallel review by FDA and Centers for Medicare & Medicaid Services. In 2011, the agencies launched the voluntary program, which could reduce the time between FDA approvals and CMS National Coverage Determinations (NCDs) (see BioCentury, June 17, 2013). Exact Sciences said it does not have a timeframe on when to expect a decision from FDA or from CMS on an NCD.

Cologuard is a non-invasive stool DNA test that utilizes a multiplexed quantitative Invader assay for the simultaneous detection of methylated and unmethylated sequences in the promoter region of the vimentin (VIM) gene. Exact Sciences has exclusive, worldwide rights from Hologic Inc. (NASDAQ:HOLX, Bedford, Mass.) to use its Invader, Invader Plus and real-time Invader detection chemistries for stool DNA-based colorectal cancer screening (see BioCentury, Oct. 26, 2009).

Epigenomics AG (Xetra:ECX), Berlin, Germany
Gamma-Dynacare Medical Laboratories, Brampton, Ontario
Quest Diagnostics Inc. (NYSE:DGX), Madison, N.J.
Sysmex Corp. (Tokyo:6869), Kobe, Japan
Abbott Laboratories (NYSE:ABT), Abbott Park, Ill.
Product: Epi proColo2.0
Business: Diagnostic

The Molecular and Clinical Genetics Panel of FDA’s Medical Devices Advisory Committee voted 5-4, with 1 abstention, that the benefits of colorectal cancer test Epi proColo 2.0 from Epigenomics outweigh the product’s risks. Concerns about the test’s efficacy were what divided the panel. After the panel voted 5-5 that Epi proColo 2.0 is effective to screen patients at average risk for colorectal cancer, the panel chair voted no to break the tie.

The panel was nearly unanimous that Epi proColo 2.0 is safe in the indication, voting 9-0 in favor, with 1 abstention. Epigenomics said it plans to meet with FDA in the next 4-6 weeks to discuss product labeling and a proposed postmarketing study for Epi proColo 2.0. The product is under Priority Review, with a decision expected this half.

Epi proColo 2.0 is a second-generation test that uses real-time PCR to detect methylated DNA of the Septin 9 gene in blood plasma. Epigenomics markets a first-generation version in Europe. In October, Epigenomics granted Polymedco Inc. (Cortlandt Manor, N.Y.) rights to jointly commercialize the test in North America (see BioCentury, Oct. 14, 2013). Epigenomics has non-exclusive licensing arrangements in place for use of the Septin 9 biomarker with Abbott, ARUP Laboratories (Salt Lake City, Utah), Gamma-Dynacare, Quest Diagnostics and Sysmex.

Exact Sciences Corp. (NASDAQ:EXAS), Madison, Wis.
Product: Cologuard stool DNA colorectal cancer screening assay
Business: Diagnostic

The Molecular and Clinical Genetics Panel of FDA’s Medical Devices Advisory Committee voted 10-0 that the benefits of Cologuard from Exact Sciences outweigh the product’s risks as an adjunctive screening test in patients who are at average risk for colorectal cancer. The panel also unanimously voted that there is reasonable assurance that Cologuard is safe and effective.
treatment. The European Commission approved the drug as add-on therapy for the indication earlier this month. The recombinant humanized mAb against IgE is also approved for the indication in Egypt, Turkey, Guatemala, El Salvador, Bangladesh, Pakistan, Ecuador and the Philippines.

Genentech and Novartis are co-developing Xolair, which is approved in over 90 countries, including the U.S. and those of the EU, as an add-on therapy to standard care to improve control of asthma in patients with severe, persistent allergic asthma. Genentech co-markets Xolair with Novartis in the U.S.

**Gilead Sciences Inc.** (NASDAQ: GILD), Foster City, Calif.  
Product: Sofosbuvir (GS-7977)/ledipasvir (GS-5885)  
Business: Infectious  
Gilead said that EMA accepted for accelerated assessment an MAA for a fixed-dose combination of Sovaldi sofosbuvir and ledipasvir to treat chronic HCV genotype 1 infection. An accelerated assessment shortens the review period to 150 days from 210. Last month, EMA’s CHMP recommended compassionate use of the combination to treat chronic HCV genotype 1 infection in patients who are at high risk of liver decompensation or death. Also last month, the company submitted an NDA to FDA for the combination (see BioCentury, Feb. 17 & Feb. 24).

The European Commission approved Sovaldi to treat chronic HCV infection in January (see BioCentury, Jan. 20). FDA and Health Canada approved the nucleotide analog HCV NS5B polymerase inhibitor in December. Ledipasvir is an HCV NS5A protein inhibitor in Phase II testing for HCV infection.

**GlaxoSmithKline plc** (LSE: GSK; NYSE: GSK), London, U.K.  
Product: Eperzan albiglutide  
Business: Endocrine/Metabolic  
The European Commission approved an MAA for Eperzan albiglutide from GlaxoSmithKline to treat Type II diabetes. The approval covers use of albiglutide as monotherapy when diet and exercise alone do not provide adequate glycemic control in patients for whom metformin is considered inappropriate; and as add-on therapy with other glucose-lowering products, including basal insulin, when these products together with diet and exercise do not provide adequate glycemic control. Eperzan is a glucagon-like peptide-1 (GLP-1) receptor agonist comprised of 2 copies of modified human GLP-1 fused in series to human albumin. A BLA for albiglutide is under FDA review, with an April 15 PDUFA date (see BioCentury, Aug. 5, 2013).

Product: Tafinlar dabrafenib (GSK2118436)  
Business: Cancer  
GlaxoSmithKline withdrew an MAA for Tafinlar dabrafenib in combination with Mekinist trametinib to treat unresectable or metastatic melanoma in adults with a BRAF V600 mutation. According to the pharma, EMA’s CHMP could not “conclude on a positive benefit-risk balance of the combination” based on data provided by GSK. The pharma said it plans to resubmit the MAA based on data from the ongoing Phase III COMBI-d and COMBI-v trials.

The European Commission approved Tafinlar as monotherapy last year; an MAA for Mekinist as monotherapy is still under review (see BioCentury, Sept. 9, 2013). Tafinlar is an oral BRAF protein kinase inhibitor, and Mekinist is a small molecule inhibitor of MAP kinase kinase 1 (MAP2K1; MEK1) and MEK2. In January, FDA approved a pair of sNDAs from GSK expanding the labels for Tafinlar and Mekinist to include their use in combination (see BioCentury, Jan. 13). FDA approved both melanoma drugs as monotherapies in May 2013. GSK in-licensed Mekinist from Japan Tobacco Inc. (Tokyo: 2914, Tokyo, Japan).

**Immucor Inc.**, Norcross, Ga.  
Product: PreciseType HEA Molecular BeadChip Test  
Business: Diagnostic  
FDA’s Blood Products Advisory Committee unanimously voted to recommend approval of a PMA from Immucor for its PreciseType HEA Molecular BeadChip Test, which utilizes genetic information of blood donors and patients to predict red blood cell, platelet and leukocyte phenotypes. Immucor expects an FDA decision on the PMA this year. The assay, which has CE Mark approval, is available in Europe and other markets for the molecular determination of allelic variants that indicate human erythrocyte antigen phenotypes in certain blood group systems as an alternative to serology. It is available in the U.S. for research use only.

**Japan Tobacco Inc.** (Tokyo:2914), Tokyo, Japan  
GlaxoSmithKline plc (LSE: GSK; NYSE: GSK), London, U.K.  
Product: Mekinist trametinib (GSK 1120212)  
Business: Cancer  
GlaxoSmithKline withdrew an MAA for Tafinlar dabrafenib in combination with Mekinist trametinib to treat unresectable or metastatic melanoma in adults with a BRAF V600 mutation. According to the pharma, EMA’s CHMP could not “conclude on a positive benefit-risk balance of the combination” based on data provided by GSK. The pharma said it plans to resubmit the MAA based on data from the ongoing Phase III COMBI-d and COMBI-v trials.

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**Kaketsuken.** Kumamoto, Japan  
GlaxoSmithKline plc (LSE: GSK; NYSE: GSK), London, U.K.  
Product: Emulsified Influenza HA Vaccine  
Business: Infectious  
Japan’s Ministry of Health, Labor and Welfare (MHLW) approved Emulsified Influenza HA Vaccine, an H5N1 adjuvanted prophylactic pandemic influenza vaccine, from Kaketsuken and partner GlaxoSmithKline. The intramuscular vaccine uses the EB66 cell line from Valneva SE (Euronext: VLA; VSE: VLA, Lyon, France), which said the approval is the first for a human vaccine using the cell line, which is derived from duck embryonic stem cells. In 2009, GlaxoSmithKline and Kaketsuken partnered to co-develop the vaccine (see BioCentury, Oct. 5, 2009).

**Med BioGene Inc.** (TSX-V: MBI), Vancouver, B.C.  
Precision Therapeutics Inc., Pittsburgh, Pa.  
Product: GeneFx Lung (formerly LungExpress Dx)  
Business: Diagnostic  
Med BioGene said Precision Therapeutics received U.S. approval to perform GeneFx Lung testing in its CLIA-certified laboratory. The 15-gene expression-based assay identifies patients with early stage non-small cell lung cancer (NSCLC) who are at higher and lower risks of mortality following surgical removal of their tumor. Med BioGene said
Precision plans to engage in “further dialogue” with payers before launching the test. Precision has exclusive, worldwide rights from Med BioGene to develop and commercialize GeneFx Lung under an April 2011 deal (see BioCentury, April 18, 2011).

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

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

Product: Xtandi enzalutamide (formerly MDV3100)

Business: Cancer

Astellas said Japan’s Ministry of Health, Labor and Welfare (MHLW) approved Xtandi enzalutamide to treat castration-resistant prostate cancer (CRPC). The pharma noted that Xtandi’s efficacy and safety has “not been established in patients with prostate cancer who have not received chemotherapy.” The Japanese approval triggered a $15 million milestone payment to partner Medivation from the pharma. The companies partnered to develop and commercialize the oral androgen receptor antagonist in 2009 (see BioCentury, Nov. 2, 2009).

Xtandi is approved in more than 35 countries, including the U.S. and those in the EU, for CRPC patients previously treated with docetaxel. Earlier this month, Astellas submitted an sNDA to FDA for Xtandi to treat chemotherapy-naïve patients with metastatic CRPC. The companies plan to submit a MAA to EMA to add the indication to the European label later this year.

**Medivir AB** (SSE:MVIR B), Huddinge, Sweden

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

Product: Sovriad simeprevir (Galexos, Olysio) (TMC435) (formerly TMC435350)

Business: Infectious

Medivir said the Russian Ministry of Health approved Sovriad simeprevir to treat HCV genotype 1 infection in combination with peginterferon alfa and ribavirin in adults with compensated liver disease who are treatment-naïve or who have failed previous interferon therapy with or without ribavirin. Johnson & Johnson already markets the second-generation HCV NS3/4A protease inhibitor in the U.S. as Olysio, in Canada as Galexos and in Japan as Sovriad to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease.

Earlier this month, EMA’s CHMP backed approval of an MAA from J&J for the product as Olysio to treat HCV genotypes 1 and 4 infection in adults in combination with other drugs, including interferon and ribavirin. Medivir expects approval in the EU next quarter (see BioCentury, March 24). J&J’s Janssen Research & Development LLC unit has ex-Nordic rights to develop and commercialize simeprevir from Medivir.

**MolMed S.p.A.** (Milan:MLM), Milan, Italy

**Takara Bio Inc.** (Tokyo:4974), Shiga, Japan

Product: TK (HSV-TK) (formerly TBI-0301)

Business: Cancer


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

Product: Bexsero

Business: Infectious

Novartis said the U.K.’s Joint Committee on Vaccination and Immunisation (JCVI) recommended the routine use on the country’s national immunization program of Bexsero in infants aged ≥2 months to prevent meningitis B infection. Novartis said the U.K. will introduce a nationwide vaccination campaign with Bexsero “as soon as possible.” The multicomponent meningococcal serogroup B vaccine is approved to vaccinate against meningococcal disease in the EU and Australia in individuals aged ≥2 months and in Canada in individuals ages 2 months through 17 years. FDA approved Bexsero under a treatment IND as part of vaccination programs at 2 universities (see BioCentury, March 3).

**Novo Nordisk A/S** (CSE:NVO; NYSE:NVO), Bagsvaerd, Denmark

Product: Tresiba insulin degludec (NN1250)

Business: Endocrine/Metabolic

EMA’s CHMP recommended expanding the label of Novo Nordisk’s Tresiba insulin degludec to include its use in combination with glucagon-like peptide-1 receptor (GLP-1R; GLP1R) agonists to treat Type II diabetes. Novo Nordisk markets Tresiba, a long-acting insulin analog, as Sovriad to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease.

Earlier this month, EMA’s CHMP backed approval of an MAA from J&J for the product as Olysio to treat HCV genotypes 1 and 4 infection in adults in combination with other drugs, including interferon and ribavirin. Medivir expects approval in the EU next quarter (see BioCentury, March 24). J&J’s Janssen Research & Development LLC unit has ex-Nordic rights to develop and commercialize simeprevir from Medivir.

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

Product: Samsca tolvaptan (formerly Samska)

Business: Renal

Otsuka said Japan’s Ministry of Health, Labor and Welfare (MHLW) approved a label expansion for Samsca tolvaptan to include treatment of autosomal dominant polycystic kidney disease (ADPKD), a rare genetic disease characterized by non-malignant cysts in the kidneys. The vasopressin 2 (V2) receptor antagonist is approved in Japan to treat fluid retention in patients with hepatic cirrhosis and volume overload in patients with heart failure (see BioCentury, Sept. 23, 2013).

Last year, FDA issued a complete response letter for the compound to slow kidney disease in adults with rapidly progressing ADPKD. Otsuka said the U.S. Food and Drug Administration will review the drug for ADPKD (see BioCentury, Aug. 30, 2013). Tolvaptan is approved in Europe to treat hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) in adults and in the U.S. to treat hypervolemic and euvoletic hyponatremia. Tolvaptan is under review in Europe for ADPKD.

**Proventus Biopharmaceuticals Inc.** (OTCQB:PVCT), Knoxville, Tenn.

See next page
Regulatory, from previous page

Product: PV-10
Business: Cancer

Provectus said it submitted a request to FDA to grant breakthrough therapy designation to PV-10 to treat melanoma. Provectus anticipates FDA’s decision within 60 days of agency receipt of the request (see BioCentury, Dec. 6, 2010 & Feb. 2, 2014). The sterile injection containing 10% rose bengal disodium completed a Phase II trial to treat recurrent melanoma and a Phase I trial to treat recurrent breast cancer. It is also in a Phase I trial for locally metastatic liver cancer. The product has Orphan Drug designation for melanoma and hepatocellular carcinoma (HCC).

Regeneron Pharmaceuticals Inc. (NASDAQ:REGN), Tarrytown, N.Y.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Product: Zaltrap aflibercept, ziv-aflibercept
Business: Cancer

The U.K.’s NICE issued final guidance recommending against the use of Zaltrap aflibercept from Sanofi in combination with FOLFIRI chemotherapy to treat metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen — its approved indication. The guidance reiterates a preliminary appraisal issued in June (see BioCentury, June 24, 2013). Sanofi appealed the final appraisal determination (FAD) in November, but NICE dismissed the appeal after a hearing on Jan. 23. The committee said Zaltrap is clinically effective but could not be considered a cost-effective use of NHS resources. Even with an undisclosed discount under a patient access scheme, NICE estimated the most plausible incremental cost-effectiveness ratio (ICER) for Zaltrap would be higher than the normally acceptable maximum ICER range of £20,000-£30,000 per quality-adjusted life year (QALY) gained.

The European Commission approved the product in February 2013 (see BioCentury, Feb. 11, 2013). Sanofi is co-developing Zaltrap, a fusion protein containing the extracellular domains from 2 VEGF receptors linked to the Fc portion of human IgG, with Regeneron.

Repros Therapeutics Inc. (NASDAQ:RPRX), The Woodlands, Texas
Product: Proellex telapristone (CDB-4124)
Business: Genitourinary

Repros said FDA provided guidance for the company’s clinical program for low-dose oral Proellex telapristone to treat uterine fibroids and endometriosis, while remaining on a partial clinical hold. The company plans to begin a 3-arm, double-blind Phase II trial of Proellex in fewer than 75 patients with uterine fibroids this year. The highest allowed dose will be 12 mg daily. Repros said it will comply with FDA guidance on the agency’s preferred efficacy endpoint — reduction in excessive menstrual bleeding associated with uterine fibroids — and said the agency noted the preferred methodology to determine changes in bleeding. Repros will also collect additional efficacy outcomes, including tumor size and other symptomatic relief. Proellex is a selective progesterone receptor modulator (SPRM).

In October 2012, Repros said FDA converted a full clinical hold on Proellex to a partial hold to allow the company to conduct a placebo-controlled Phase II trial evaluating low-dose Proellex to treat severe endometriosis (see BioCentury, Oct. 15, 2012). In 2010, FDA replaced a full clinical hold on Proellex with a partial hold so that Repros could evaluate up to 12 mg of Proellex in a Phase II trial to treat uterine fibroids, endometriosis, painful menses, cramping and menorrhagia. FDA put the oral Proellex program on hold in 2009 after clinically significant increases in liver enzymes were observed at doses of 25 and 50 mg in Phase III trials. Before the clinical hold, Proellex was in Phase III testing to treat uterine fibroids and anemia associated with uterine fibroids, and was in Phase II testing for endometriosis (see BioCentury, June 14, 2010).

Rockwell Medical Inc. (NASDAQ: RMTI), Wixom, Mich.
Product: Triferic soluble ferric pyrophosphate citrate (Soluble Ferric Pyrophosphate (SFP))
Business: Hematology

Rockwell Medical submitted an NDA to FDA for Triferic soluble ferric pyrophosphate citrate to treat iron deficiency in chronic kidney disease (CKD) patients receiving hemodialysis. Triferic is a soluble form of iron in liquid bicitrate.

Taiho Pharmaceutical Co. Ltd., Tokyo, Japan
Product: Lonsurf trifluridine/tipiracil (TAS-102)
Business: Cancer

Japan’s Ministry of Health, Labor and Welfare (MHLW) approved Lonsurf trifluridine/tipiracil from Taiho to treat unresectable advanced or recurrent colorectal cancer refractory to standard therapies. Taiho said it plans to launch Lonsurf once Japan’s National Health Insurance determines a price, which is expected in late May. The company said approval was based on primarily on data from a double-blind, placebo-controlled, Japanese Phase II trial of Lonsurf. Taiho is conducting the international Phase III RECOUSE trial of the product in patients with metastatic colorectal cancer refractory to standard chemotherapies.

The company said it plans to seek approval for Lonsurf in the U.S., EU and Asia but has not yet determined the timing. The product is also in Phase II testing in Japan and the EU to treat small cell lung cancer (SCLC). Lonsurf is an oral nucleoside antitumor agent composed of a mixture of trifluorothymidine (FTD) and 5-chloro-6-(2-iminopyrrolidin-1-yl)-methyl-2,4(1H,3H)-pyrimidinedione hydrochloride (TPI). Taiho is a subsidiary of Otsuka Holdings Co. Ltd. (Tokyo:4578, Tokyo, Japan).

Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
Product: Zacras azilsartan/amlopidine besylate
Business: Cardiovascular

Takeda said Japan’s Ministry of Health, Labor and Welfare (MHLW) approved an NDA for Zacras, a fixed-dose combination of azilsartan and amlopidine besylate, to treat hypertension. Azilha azilsartan, a once-daily angiotensin II type 1 (AT1) receptor (AGTR1) antagonist, is marketed in Japan and is approved in the U.S. and EU for hypertension.

Product: Takelda lansoprazole/aspirin
Business: Gastrointestinal

Takeda said Japan’s Ministry of Health, Labor and Welfare (MHLW) approved an NDA for Takelda lansoprazole/aspirin to reduce the risk of thrombosis and embolism in patients who have a history of gastric and duodenal ulcer. Specifically, the fixed-dose combination of Takeda’s lansoprazole and low-dose aspirin is indicated in patients who have had angina, myocardial infarction (MI) and ischemic cerebrovascular disease and patients who have had coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Takeda markets lansoprazole, a benzimidazole proton pump inhibitor (PPI), as Takeprin in Japan and as Prevacid in the U.S. for gastric and duodenal ulcers.

Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Product: Velcade bortezomib
Regulatory, from previous page

**Business: Cancer**

The U.K.’s NICE issued a final appraisal determination (FAD) now recommending the use of Velcade bortezomib from Johnson & Johnson in combination with dexamethasone or in combination with dexamethasone and thalidomide for induction treatment of adults with previously untreated multiple myeloma (MM) who are eligible for high-dose chemotherapy with hematopoietic stem cell transplantation (HSCT). The FAD reverses draft guidance issued in November, in which NICE recommended against the use of Velcade in combination with thalidomide and dexamethasone for induction treatment in the population. NICE also minded not to recommend the drug for the indication in combination with dexamethasone and requested further evidence on the clinical and cost-effectiveness of the combination therapy compared with standard of care (SOC) (see BioCentury, Nov. 18, 2013). The European Commission expanded the label of Velcade to include the 2 indications last year. NICE said that the most plausible incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) for Velcade plus dexamethasone with or without thalidomide compared with the SOC was “likely to be below” £30,000 ($49,908). The committee usually considers products with ICERs less than or equal to £30,000 per QALY to be cost-effective. Velcade plus dexamethasone and thalidomide was compared with thalidomide and dexamethasone as the SOC. Velcade plus dexamethasone was compared with cyclophosphamide, thalidomide and dexamethasone and with vinorelbine, doxorubicin and dexamethasone as the SOC.

The small molecule dipeptide boronic acid proteasome inhibitor is also approved in the EU for previously untreated MM patients who are not eligible for high-dose chemotherapy with bone marrow transplantation in combination with melphalan and prednisone and as monotherapy for progressive MM in patients who have received ≥1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation. Takeda’s Millennium Pharmaceuticals Inc. subsidiary markets Velcade in the U.S. to treat MM and mantle cell lymphoma (MCL), while J&J has rights elsewhere.

**United Therapeutics Corp.** (NASDAQ:UTHR), Silver Spring, Md.

**Product:** Treprostin treprostinil (Remodulin) (MD-0701)

**Business:** Cardiovascular

United Therapeutics’ inhaled prostanoid has received an expanded indication in Japan for the treatment of PAH. The U.K. Ministry of Health, Labor and Welfare (MHLW) approved subcutaneous and IV Treprostin treprostinil to treat pulmonary arterial hypertension (PAH). Mochida Pharmaceutical Co. Ltd. (Tokyo:4534, Tokyo, Japan) will commercialize the drug in Japan, with a pricing decision from Japan’s National Health Insurance Co. Ltd. (Tokyo:4507, Osaka, Japan) planned for later this year. The application was submitted under section 505(b)(2) of the Food, Drug and Cosmetic Act, which allows sponsors to reference data on safety and efficacy from scientific literature or from previously approved products. Actavis acquired worldwide rights to the topical nitroimidazole antibiotic from Valeant in April 2013 (see BioCentury, May 6, 2013).

**ViiV Healthcare Ltd.,** Brentford, U.K.

**Product:** Tivicay dolutegravir (S/GSK1349572) (formerly S-349572)

**Business:** Infectious


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<td><strong>Andrus Reo Ltd.,</strong> Moscow, Russia</td>
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<td><strong>Oncolytics Biotech Inc.</strong> (TSX:ONC; NASDAQ:ONCY), Calgary, Alberta</td>
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**Product:** Reolysin

**Business:** Cancer

**Molecular target:** Not applicable

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

**Indication:** Treat metastatic colorectal cancer (mCRC) in patients with K-Ras (KRAS) mutations

**Endpoint:** Dose-limiting toxicities (DLTs) and recommended Phase II dose; objective response rate (ORR), clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS) and safety

**Status:** Preliminary Phase I data

**Milestone:** NA

Preliminary data from the single-arm, open-label, dose-escalation, U.S. Phase I REO 022 trial in 18 evaluable patients with oxaliplatin-refractory mutant KRAS mCRC showed that IV Reolysin on days 1-5 of a 28-day cycle plus FOLFIRI chemotherapy led to 1 partial response plus 9 cases of stable disease. Median PFS in FOLFIRI-naïve patients was 7.4 months and median PFS in patients who previously received FOLFIRI has not yet been reached. The combination was well tolerated with neutropenia, anemia and thrombocytopenia reported as the most common grade 3/4 adverse events. There was 1 death due to acute renal failure that was unrelated to treatment. Data were presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium in San Francisco. Reolysin is also in Phase III testing to treat platinum-refractory head and neck cancer and Phase II testing for multiple other cancer indications. Last year, Oncolytics granted Andrus Reo rights to Reolysin in the Commonwealth of Independent States (CIS) (see BioCentury, Feb. 25, 2013).

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

**Product:** Asunaprevir (BMS-650032)

**Business:** Infectious

**Molecular target:** HCV NS3 protease

**Description:** HCV NS3 protease inhibitor

**Indication:** Treat HCV genotype 1b infection

**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:** Submit NDA (1H14); Additional Phase II data (04/2014)

The double-blind, placebo-controlled, international Phase III HALL-
MARK DUAL (AI447028) trial in 643 patients with HCV genotype 1b infection showed that once-daily 60 mg oral daclatasvir plus twice-daily 100 mg oral asunaprevir for 24 weeks led to an SVR 12 weeks after the end of treatment in 90% of treatment-naive patients (n=203), 82% of prior null or partial responders to peginterferon and ribavirin (n=205) and 82% of patients who were ineligible for or intolerant to peginterferon and ribavirin (n=235). SVR12 rates were 85% in non-cirrhotic patients (n=437) and 84% in cirrhotic patients (n=206). There were 9 cases of virologic breakthrough in treatment-naive patients, 26 cases in null/partial responders and 20 cases in ineligible/intolerant patients. Daclatasvir plus asunaprevir was generally well tolerated. Treatment-naive patients received daclatasvir plus asunaprevir for 24 weeks or placebo for 12 weeks; placebo patients then received daclatasvir plus asunaprevir in another trial. Data will be presented at the European Association for the Study of the Liver meeting in London in April.

Daclatasvir plus asunaprevir has breakthrough therapy designation from FDA to treat HCV genotype 1b infection. Bristol-Myers said the designation is based on data from HALLMARK DUAL (see BioCentury, March 3). In January, EMA accepted for review and granted accelerated assessment to an MAA for daclatasvir to treat HCV infection in patients with decompensated liver disease, including HCV genotypes 1, 2, 3 and 4 infection (see BioCentury, Jan. 13). This half, the pharma plans to submit separate NDAs to FDA for daclatasvir and asunaprevir.

Last November, Bristol-Myers submitted an NDA to Japan’s Ministry of Health, Labor and Welfare (MHLW) for an interferon- and ribavirin-free oral regimen of daclatasvir and asunaprevir to treat chronic HCV genotype 1b infection at the time of submission, Bristol-Myers reported data from an open-label, Japanese Phase III trial in 222 patients with HCV genotype 1b infection who were either ineligible or intolerant to interferon or were non-responders to interferon and ribavirin showing that daclatasvir plus asunaprevir led to an SVR24 in 84.7% of patients. Daclatasvir is a selective HCV NS5A protein inhibitor. Roche (SIX:ROG; OTCQX:RHHBY, Basel, Switzerland) markets Pegasys peginterferon alfa-2a and Copegus ribavirin.

Product: Daclatasvir (BMS-790052)
Business: Infectious
Molecular target: HCV NS5A protein
Description: Selective HCV NS5A protein inhibitor
Indication: Treat HCV genotype 1 infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment
Status: Phase IIa data
Milestone: Submit NDA (1H14); complete Phase II (05/2015)

Medivir AB (SSE:MMVIR, Sweden) reported data from the open-label Phase IIa LEAGUE-I (AI444-062) trial in 147 patients with HCV genotype 1b infection showing that once-daily oral combinations of 150 mg simeprevir plus 30 mg daclatasvir with or without ribavirin for 12 or 24 weeks led to an SVR 12 weeks after the end of treatment in 75-85% of treatment-naive patients (n=104) and in 65-95% of prior null responders (n=43). Fifteen patients with HCV genotype 1b infection experienced virologic breakthrough. An exploratory analysis of treatment-naive patients with HCV genotype 1a infection (n=12) showed that simeprevir plus daclatasvir with ribavirin for 24 weeks led to an SVR12 rate of 67%. Four patients with HCV genotype 1a infection experienced virologic breakthrough. The combination with and without ribavirin was generally well tolerated. Data were presented at the Conference on Retroviruses and Opportunistic Infections meeting in Boston. Medivir said further studies are required in order to fully assess the potential of the simeprevir/daclatasvir combination, but could not be reached for details.

Johnson & Johnson (NYSE:JNJ, New Brunswick, N.J.) said its collaboration agreement with Bristol-Myers for the daclatasvir/simeprevir combination is limited to Phase II testing and that the partners do not have plans for Phase III testing at this time. J&J’s Janssen Research & Development LLC is conducting a Phase II trial with the combination in post-liver transplant patients with HCV genotype 1b infection which is slated to complete in May 2015.

J&J markets simeprevir in the U.S. as Olysio, in Canada as Galexos and in Japan as Soviad to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. Earlier this month, EMA’s CHMP backed approval of an MAA for Olysio to treat HCV genotypes 1 and 4 infection in adults in combination with other drugs, including interferon and ribavirin (see BioCentury, March 24). Janssen has ex-Nordic rights to develop and commercialize the HCV NS3/4A protease inhibitor from Medivir.

In January, EMA accepted for review and granted accelerated assessment to an MAA from Bristol-Myers for daclatasvir to treat HCV infection in patients with decompensated liver disease, including HCV genotypes 1, 2, 3 and 4 infection (see BioCentury, Jan. 13). This half, the pharma plans to submit an NDA to FDA for daclatasvir. Roche (SIX:ROG; OTCQX:RHHBY, Basel, Switzerland) markets Copegus ribavirin.

Indication: Treat HCV genotype 1b infection
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: Submit NDA (1H14); additional Phase III data (04/2014)

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patients with HCV genotype 1b infection who were either ineligible or intolerant to interferon or were non-responders to interferon and ribavirin, showing that daclatasvir plus asunaprevir led to an SVR24 in 84.7% of patients. Asunaprevir is an HCV NS3 protease inhibitor. Roche (SIX:ROG; OTCQX: RHHBY, Basel, Switzerland) markets Pegasys peginterferon alfa-2a and Copegus ribavirin.

Galderma S.A., Lausanne, Switzerland
Product: Ivermectin 1% (CD5024 1%)  
Business: Dermatology  
Molecular target: NA  
Description: 1% formulation of ivermectin, a macrocyclic lactone derivative  
Indication: Treat papulopustular rosacea  
Endpoint: Proportion of patients who achieve “clear” or “almost clear” at week 12 based on an Investigator Global Assessment (IGA) score and absolute change in inflammatory lesion count from baseline to week 12  
Status: Phase III data  
Milestone: NDA action (2014)

The identical, double-blind, North American Phase III Study 1 and Study 2 in patients with papulopustular rosacea showed that once-daily ivermectin 1% cream met the co-primary end points in both trials of improving the proportion of patients rated as “clear” or “almost clear” based on an IGA score (Study 1: 38.4% vs. 11.6%; Study 2: 40.1% vs. 18.8%) and of reducing median inflammatory lesion count from baseline to week 12 (Study 1: 76% vs. 50%; Study 2: 75% vs. 50%) vs. placebo (p<0.001 for all). For all endpoints, Galderma also said ivermectin 1% was significantly superior to placebo starting at week 4 (p<0.001). There were no treatment-related serious adverse events. The most common treatment-related adverse event was sensation of skin burning in Study 1 and pruritus and dry skin in Study 2. Study 1 enrolled 683 patients and Study 2 enrolled 688 patients. Data were presented at the American Academy of Dermatology meeting in Denver and published in the Journal of Drugs in Dermatology.

Galderma submitted an NDA to FDA for ivermectin 1% to treat papulopustular rosacea in December. The company said it expects a decision from FDA before year end, but a specific PDUFA date is not disclosed. Sanofi (Euronext:SAN; NYSE:SNY, Paris, France) markets a 0.5% formulation of ivermectin in the U.S. as Sklice to treat head lice.

Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.
Product: GS-5816  
Business: Infectious  
Molecular target: HCV NS5A protein  
Description: Oral pan-genotypic HCV NS5A inhibitor  
Indication: Treat HCV infection  
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after end of treatment; SVR4, SVR24 and virologic failure  
Status: Phase II data  
Milestone: Additional Phase II data (04/2014); start Phase III (2H14)

A Phase II trial in 154 treatment-naïve patients with HCV genotypes 1-6 infection without cirrhosis showed that once-daily 400 mg Sovaldi plus once-daily 25 or 100 mg GS-5816 for 12 weeks led to an SVR 4 weeks after end of treatment in 96% of patients. Specifically, SVR4 rates were 96% for the low-dose GS-5816 arm and 100% for the high-dose GS-5816 arm in patients with HCV genotype 1 infection; 91% for the low-dose GS-5816 arm and 100% for the high-dose GS-5816 arm in patients with HCV genotype 2 infection; 89% for the low-dose GS-5816 arm and 100% for the high-dose GS-5816 arm in patients with HCV genotype 3 infection; 100% for the low-dose GS-5816 arm and 86% for the high-dose GS-5816 arm in patients with HCV genotype 4 infection; 100% for the low-dose GS-5816 arm in patients with HCV genotype 5 infection (no patients with HCV genotype 5 infection received high-dose GS-5816); and 100% for both GS-5816 arms in patients with HCV genotype 6 infection.

Two patients relapsed in the low-dose GS-5816 arm — 1 with HCV genotype 1 infection and 1 with HCV genotype 3 infection. The combination was well tolerated with fatigue, headache and nausea reported as the most common adverse events. Data will be presented at the European Association for the Study of the Liver meeting in London in April. Next half, Gilead plans to start Phase III testing with the combination. Gilead markets Sovaldi, a nucleotide analog HCV NS5B polymerase inhibitor in the U.S., EU and Canada to treat HCV infection.

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  
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after end of treatment; SVR4, SVR24 and virologic failure  
Status: Phase II data  
Milestone: Additional Phase II data (04/2014); start Phase III (2H14)

A Phase II trial in 154 treatment-naïve patients with HCV genotypes 1-6 infection without cirrhosis showed that once-daily 400 mg Sovaldi plus once-daily 25 or 100 mg GS-5816 for 12 weeks led to an SVR 4 weeks after end of treatment in 96% of patients. Specifically, SVR4 rates were 96% for the low-dose GS-5816 arm and 100% for the high-dose GS-5816 arm in patients with HCV genotype 1 infection; 91% for the low-dose GS-5816 arm and 100% for the high-dose GS-5816 arm in patients with HCV genotype 2 infection; 89% for the low-dose GS-5816 arm and 100% for the high-dose GS-5816 arm in patients with HCV genotype 3 infection; 100% for the low-dose GS-5816 arm and 86% for the high-dose GS-5816 arm in patients with HCV genotype 4 infection; 100% for the low-dose GS-5816 arm in patients with HCV genotype 5 infection (no patients with HCV genotype 5 infection received high-dose GS-5816); and 100% for both GS-5816 arms in patients with HCV genotype 6 infection.

Two patients relapsed in the low-dose GS-5816 arm — 1 with HCV genotype 1 infection and 1 with HCV genotype 3 infection. The combination was well tolerated with fatigue, headache and nausea reported as the most common adverse events. Data will be presented at the European Association for the Study of the Liver meeting in London in April. Next half, Gilead plans to start Phase III testing with the combination. Gilead markets Sovaldi, a nucleotide analog HCV NS5B polymerase inhibitor in the U.S., EU and Canada to treat HCV infection.

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Product: Votrient pazopanib  
Business: Cancer  
Molecular target: Vascular endothelial growth factor (VEGF) receptor 1 (FLT1) (VEGFR-1); Vascular endothelial growth factor (VEGF) receptor 2 (KDR/Fk-1) (VEGFR-2)  
Description: Broad-spectrum inhibitor of VEGF and other tyrosine kinases  
Indication: Treat advanced solid tumors  
Endpoint: Maximum tolerated dose (MTD) and safety; pharmacokinetics and objective response rate (ORR)  
Status: Phase I data  
Milestone: NA  
Researchers at the Dana-Farber Cancer Institute and colleagues

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reported data from an open-label, U.S. Phase I trial in 9 patients with advanced solid tumors showing that pazopanib plus everolimus led to a complete response lasting for 14 months in 1 patient with bladder cancer plus 4 cases of stable disease — 3 patients with bladder cancer and 1 patient with adrenal gland cancer. Genomic profiling of the bladder cancer patient’s tumor identified 2 mutations — mTOR E2419K and mTOR E2014K. The researchers said the mutations likely rendered the patient’s cancer dependent on the mammalian target of rapamycin (mTOR; FRAP; RAFT1) pathway to survive and is the likely reason the cancer became sensitive to everolimus. Data were published in Cancer Discovery. The trial was funded by the Broad Institute, the National Human Genome Research Institute, GlaxoSmithKline and Novartis AG (NYSE:NVS; SIX:NOVN, Basel, Switzerland). Novartis said it has no plans for additional studies with everolimus and pazopanib in bladder cancer, while GSK could not be reached for comment.

GlaxoSmithKline markets pazopanib as Votrient, and Novartis markets everolimus, an oral mTOR protein inhibitor, as Afinitor.

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

Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan

Product: GWP42006

Business: Neurology

Molecular target: Cannabinoid receptors

Description: Non-psychoactive cannabinoid cannabidiivar (CBDV) extracted from specific chemotypes of the cannabis plant

Indication: Treat epilepsy

Endpoint: Safety; pharmacokinetics, cognitive function and gene expression

Status: Phase I data

Milestone: Start Phase II (2014)

A double-blind, placebo-controlled, U.K. Phase I trial in 66 healthy volunteers showed that single and multiple doses of 25, 75, 200 and 400 mg oral GWP42006 were well tolerated with no serious adverse events or withdrawals due to adverse events reported. In the multiple dose arms, GWP42006 was given once, twice or thrice daily for 5 days. This year, GW plans to start a Phase II trial with GWP42006 to treat epilepsy. GW and Otsuka partnered in 2007 to evaluate cannabinoid compounds for CNS disorders and cancer (see BioCentury, July 16, 2007).

Hua Medicine Ltd., Shanghai, China

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

Product: HMS5552, ROS305552

Business: Endocrine/Metabolic

Molecular target: Glucokinase (GCK) (GK)

Description: Small molecule glucokinase (GCK; GK) activator

Indication: Treat Type II diabetes

Endpoint: Safety; pharmacokinetics and fasting plasma glucose (FPG) levels

Status: Phase Ia data

Milestone: Complete Phase Ib (3Q14)

A double-blind, placebo-controlled, Chinese Phase Ia trial in 60 healthy volunteers showed that single doses of 5-50 mg oral HMS5552 were well tolerated. The total adverse event rate was identical between HMS5552 and placebo with no severe adverse events, death, premature withdrawals due to adverse events or significant laboratory, vital signs or ECG abnormalities reported. HMS5552 also led to dose-proportional increases in post-meal insulin and glucagon-like peptide-1 (GLP-1) that were “notably above placebo” levels. HMS5552 also led to dose-proportional reductions in FPG without hypoglycemia or significant changes in other regulatory hormones. Hua Medicine said the data have been submitted for presentation at the American Diabetes Association meeting in San Francisco in June. Hua Medicine is also conducting a Phase Ib trial evaluating multiple ascending-doses of HMS5552 in Type II diabetics. The Phase Ib trial is expected to complete by 3Q14. The company has exclusive, worldwide rights to develop and commercialize Roche’s GCK activator program, including HMS5552, under a 2011 deal (see BioCentury, Jan. 2, 2012).

Idera Pharmaceuticals Inc. (NASDAQ:IDRA), Cambridge, Mass.

Product: IMO-8400

Business: Autoimmune

Molecular target: Toll-like receptor 7 (TLR7); Toll-like receptor 8 (TLR8)

Description: Toll-like receptor 7 (TLR7), TLR8 and TLR9 antagonist

Indication: Treat moderate to severe plaque psoriasis

Endpoint: Safety; Psoriasis Area and Severity Index (PASI) 50 and 75 responses

Status: Phase II data

Milestone: Additional Phase II data (2Q14)

Top-line data from a double-blind, placebo-controlled, Dutch Phase II trial in 32 patients with moderate to severe plaque psoriasis showed that once-weekly 0.075, 0.15 and 0.3 mg/kg subcutaneous IMO-8400 for 12 weeks each met the primary endpoint of safety. Specifically, all 3 doses of IMO-8400 were well tolerated with no treatment-related discontinuation, serious adverse events or dose reductions reported. IMO-8400 also met the secondary endpoint of demonstrating clinical activity as measured by PASI responses. In patients who completed 12 weeks of treatment (n=27), IMO-8400 led to a PASI 50 response rate of 45% vs. 14% for placebo and a PASI 75 response rate of 20% vs. 0% for placebo.

Last October, Idera expanded the trial to evaluate a once-weekly 0.6 mg/kg dose of IMO-8400 or placebo in 12 patients. Data from the expansion cohort are expected by the end of next quarter. IMO-8400 is also in a Phase I/II trial to treat Waldenstrom’s macroglobulinemia. Next half, Idera plans to start a pair of Phase I/II trials with the compound to treat diffuse large B cell lymphoma (DLBCL) and polymyositis/dermatomyositis, respectively.

Insmed Inc. (NASDAQ:INSM), Monmouth Junction, N.J.

Product: Arikayce amikacin (Arikace) (formerly SLIT amikacin)

Business: Infectious

Molecular target: Ribosomal 30S subunit

Description: Inhaled liposomal amikacin

Indication: Treat non-tuberculosis mycobacterial (NTM) lung infection

Endpoint: Change from baseline in mycobacterial density at 84 days; proportion of patients with culture conversion to negative, time to rescue anti-mycobacterial drugs, 6-minute walk distance (6MWD), oxygen saturation, Patient-Reported Outcomes and safety

Status: Phase II data

Milestone: Additional Phase II data (05/2014)

The double-blind, North American Phase II TARGET NTM (TR02-112) trial in 89 evaluable patients with treatment-resistant NTM lung infection showed that once-daily 560 mg Arikayce administered with the eFlow Nebulizer System from Pari GmbH (Starnberg, Germany) plus standard of care (SOC) missed the primary endpoint of reducing mycobacterial density as measured by a 7-point scale from baseline to day 84 vs. placebo plus SOC (p=0.148). Arikayce plus SOC did meet the secondary endpoint of a greater proportion of patients with culture conversion to negative by day 84 vs. placebo plus SOC (25% vs. 7%, p=0.01).
Patients receiving Arikayce also experienced a greater number of treatment-emergent adverse events vs. patients receiving placebo (240 vs. 140 events). The most common side effect was laryngeal irritation. Following the double-blind portion of the trial, all patients had the option to receive Arikayce in an 84-day, open-label extension. Additional data will be presented at the American Thoracic Society meeting in San Diego in May. Insmed plans to meet with FDA and EMA to determine next steps for Arikayce to treat NTM lung infection. Insmed also said it plans to apply for breakthrough therapy designation in the U.S. for Arikayce in the indication based on the culture conversion data in TARGET NTM.

This half, Insmed plans to submit regulatory applications to EMA and Health Canada for Arikayce to treat Pseudomonas aeruginosa infection in cystic fibrosis (CF) patients. In 2012, FDA lifted the clinical hold on development of Arikayce in CF patients with P. aeruginosa lung infection (see BioCentury, May 14, 2012). Arikayce has Orphan Drug designation in the U.S. and Europe to treat P. aeruginosa infection in patients with CF. Orphan Drug designation in the U.S. to treat bronchiectasis in patients with P. aeruginosa infection, and Qualified Infectious Disease Product (QIDP), Orphan Drug and Fast Track designations in the U.S. and Orphan Drug designation in the EU to treat NTM lung infection. Insmed gained Arikayce through its 2010 acquisition of Transave Inc. (see BioCentury, Dec. 6, 2010).

Med BioGene Inc. (TSX-V:MBI), Vancouver, B.C.

Precision Therapeutics Inc., Pittsburgh, Pa.

Product: GeneFx Lung (formerly LungExpress Dx)

Business: Diagnostic

Molecular target: NA

Description: 15-gene expression-based assay that identifies patients with early stage non-small cell lung cancer (NSCLC) who are at higher and lower risks of mortality following surgical removal of their tumor

Indication: Classify patients with early stage non-small cell lung cancer (NSCLC) who are at higher and lower risks of mortality following surgical removal of their tumor

Endpoint: Estimate 5-year overall survival (OS) probabilities

Status: NA data

Milestone: NA

A validation study analyzing 181 frozen, resected stage I/II NSCLC tumor specimens showed that Med BioGene’s GeneFx Lung classified the samples into high- and low-risk prognostic groups with significantly different OS (p=0.012). In a subgroup analysis, the test predicted survival in 127 stage I patients (p=0.018) as well as in a smaller subgroup of 48 stage IA patients (p=0.014). Furthermore, the test was prognostic for both adenocarcinoma (p=0.058) and squamous cell carcinoma (SCC) cases (p=0.045). Data were published in the Journal of Thoracic Oncology.

On March 24, MedBioGene said Precision Therapeutics received U.S. approval to perform GeneFx Lung testing in its CLIA-certified laboratory. MedBioGene said Precision plans to engage in “further dialogue” with payers before launching the test. Precision has exclusive, worldwide rights from Med BioGene to develop and commercialize GeneFx Lung under an April 2011 deal (see BioCentury, April 18, 2011).

Medivir AB (SSE:MYIR B), Huddinge, Sweden

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

Product: Simeprevir (Olysio, Galexos, Sovriad) (TMC435) (formerly TMC435350)

Business: Infectious

Molecular target: HCV NS3/4A protease complex

Description: HCV NS3/4A protease inhibitor

Indication: Treat HCV genotype 1 infection

Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment

Status: Phase IIa data

Milestone: Complete Phase II (05/2015)

Medivir reported data from the open-label Phase IIa LEAGUE-I (AI444-062) trial in 147 patients with HCV genotype 1b infection showing that once-daily oral combinations of 150 mg simeprevir plus 30 mg daclatasvir with or without ribavirin for 12 or 24 weeks led to an SVR 12 weeks after the end of treatment in 75-85% of treatment-naïve patients (n=104) and in 65-95% of prior null responders (n=43). Fifteen patients with HCV genotype 1b infection experienced virologic breakthrough. An exploratory analysis of treatment-naïve patients with HCV genotype 1a infection (n=12) showed that simeprevir plus daclatasvir with ribavirin for 24 weeks led to an SVR 12 rate of 67%. Four patients with HCV genotype 1a infection experienced virologic breakthrough. The combination with and without ribavirin was generally well tolerated. Data were presented at the Conference on Retroviruses and Opportunistic Infections meeting in Boston.

Medivir said further studies are required in order to fully assess the potential of the simeprevir/daclatasvir combination, but could not be reached for details. Johnson & Johnson said its collaboration agreement with Bristol-Myers Squibb Co. (NYSE:BMY, New York, N.Y.) for the daclatasvir/simeprevir combination is limited to Phase II testing and that the partners do not have plans for Phase III testing at this time. J&J’s Janssen Research & Development LLC is conducting a Phase II trial with the combination in post-liver transplant patients with HCV genotype 1b infection which is slated to complete in May 2015.

J&J markets simeprevir in the U.S. as Olysio, in Canada as Galexos and in Japan as Sovriad to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. Earlier this month, EMA’s CHMP backed approval of an MAA for Olysio to treat HCV genotypes 1 and 4 infection in adults in combination with other drugs, including interferon and ribavirin (see BioCentury, March 24). Janssen has ex-Nordic rights to develop and commercialize simeprevir from Medivir.

In January, EMA accepted for review and granted accelerated assessment to an MAA from Bristol-Myers for daclatasvir to treat HCV infection in patients with decompensated liver disease, including HCV genotypes 1, 2, 3 and 4 infection (see BioCentury, Jan. 13). This half, the pharma plans to submit an NDA to FDA for the selective HCV NSSA protein inhibitor. Roche (SIX:ROG; OTCQX:RHHBY, Basel, Switzerland) markets Copegus ribavirin.

Indication: Treat chronic HCV genotype 1 infection

Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after the end of treatment

Status: Phase III data

Milestone: NA

The double-blind Phase III ATTAIN trial in 771 treatment-experienced patients with chronic HCV genotype 1 infection and compensated liver disease showed that once-daily 150 mg simeprevir plus peginterferon and ribavirin for 12 weeks followed by peginterferon and ribavirin alone for 36 weeks met the primary endpoint of non-inferiority to thrice-daily 750 mg Incivek telaprevir plus peginterferon and ribavirin for 12 weeks followed by peginterferon and ribavirin alone for 36 weeks in the proportion of patients with an SVR 12 weeks after the end of treatment (54% vs. 55%). In prior null responders, the SVR12 rate was 44% in the simeprevir arm vs. 46% in the Incivek arm. In prior partial responders, the SVR12 rate was 70% in the simeprevir arm vs. 69% in the Incivek arm. Data were presented at the Asian Pacific Association...
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for the Study of the Liver meeting in Brisbane.

Johnson & Johnson markets simprevir in the U.S. as Olysio, in Canada as Galexs and in Japan as Sovriad to treat chronic HCV genotype 1 infection in combination with interferon and ribavirin in patients with compensated liver disease. Earlier this month, EMA’s CHMP backed approval of an MAA for Olysio to treat HCV genotypes 1 and 4 infection in adults in combination with other drugs, including interferon and ribavirin (see BioCentury, March 24). J&J’s Janssen Research & Development LLC unit has ex-Nordic rights to develop and commercialize simprevir from Medivir. Vertex Pharmaceuticals Inc. (NASDAQ:VRTX, Boston, Mass.) markets Incivek. Roche (SIX:ROG; OTCQX:RHHBY, Basel, Switzerland) markets Pegasys peginterferon alfa-2a and Copegus ribavirin.

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 psoriasis
Endpoint: Physician’s Global Assessment (PGA) score of “cleared” or “minimal” at week 16; proportion of patients achieving a Psoriasis Area and Severity Index (PASI) 75 response or greater and change from baseline in Dermatology Life Quality Index (DLQI)
Status: Phase Ib/Ib data
Milestone: Start Phase III (2014)

The double-blind, international Phase IIb X-PLORE trial in 293 patients with moderate to severe plaque psoriasis showed that all doses of subcutaneous guselkumab met the primary endpoint of a greater proportion of patients achieving a PGA score of “cleared” or “minimal” at week 16 vs. placebo. Specifically, the proportion of patients achieving a PGA score of “cleared” or “minimal” at week 16 was 62% in the 100 mg guselkumab; and 57% in the 200 mg guselkumab vs. 34% in the 15 mg guselkumab arm; 45% in the 50 mg guselkumab arm; 61% in the 15 mg guselkumab every 8 weeks arm; 79% in the 100 mg guselkumab at weeks 0 and 4 and then every 12 weeks arm; 86% in the 100 mg guselkumab every 8 weeks arm; and 83% in the 200 mg at weeks 0 and 4 and then every 12 weeks arm vs. 7% for placebo (p<0.001 for all other doses). Additionally, 58% of patients receiving 80 mg subcutaneous Humira adalimumab at week 0 followed by 40 mg every other week achieved the primary endpoint. Johnson & Johnson said the trial was not powered to show superiority to Humira.

All doses of guselkumab also met the secondary endpoint of a greater proportion of patients achieving a PASI 75 response or greater at week 16 vs. placebo (p<0.001). Specifically, the proportion of patients achieving a PASI 75 response or greater at week 16 was 44% in the 5 mg guselkumab arm; 76% in the 15 mg guselkumab arm; 81% in the 50 mg guselkumab arm; 79% in the 100 mg guselkumab; and 81% in the 200 mg guselkumab vs. 5% for placebo. Furthermore, all doses of guselkumab met the secondary endpoint of a greater proportion of patients achieving a PASI 90 response or greater at week 16 vs. placebo (p<0.001). Specifically, the proportion of patients achieving a PASI 90 response or greater at week 16 was 34% in the 5 mg guselkumab arm; 34% in the 15 mg guselkumab arm; 45% in the 50 mg guselkumab arm; 62% in the 100 mg guselkumab; and 57% in the 200 mg guselkumab vs. 2% for placebo. Additionally, 70% of patients in the Humira arm achieved a PASI 75 response and 44% achieved a PASI 90 response.

J&J’s Janssen Research & Development LLC unit also said the proportions of patients achieving a PGA score of “cleared” or “minimal,” a PASI 75 response and a PASI 90 response remained consistent or showed additional improvement for guselkumab through week 40. Through week 16, serious infections of appendicitis and lung abscess occurred in 2 patients receiving guselkumab, with no malignancies or major adverse cardiovascular events (MACE) reported in any treatment arm. Through week 52, 1 guselkumab-treated patient reported a malignancy (cervical intraepithelial neoplasia (CIN) 3) and there were 3 cases of MACE reported in guselkumab-treated patients, all of whom had multiple pre-existing cardiovascular risk factors. Data were presented at the American Academy of Dermatology meeting in Denver. This year, Janssen plans to start Phase III testing with guselkumab to treat psoriasis.

Data from a Phase II trial evaluating guselkumab compared to J&J’s Stelara ustekinumab to treat rheumatoid arthritis (RA) are expected in H114. Janssen and MorphoSys are partnered under a 2000 deal in which MorphoSys used its HuCAL human combinatorial antibody library to generate antibodies for a range of indications and perform target discovery for Janssen. Guselkumab was discovered under the deal. The discovery portion of the deal expired in late 2007 and MorphoSys is eligible for milestones and royalties (see BioCentury, Jan. 8, 2001). Stelara, a human mAb targeting the p40 subunit of IL-23 and IL-12, is approved in at least 74 countries, including the U.S., Canada and those in the EU, to treat moderate to severe plaque psoriasis in adults. AbbVie Inc. (NYSE:ABBV, Chicago, Ill.) markets Humira.

Novan Inc., Durham, N.C.
Product: SB204, NVN1000
Business: Dermatology
Molecular target: Androgen receptor
Description: Nitric oxide (NO)-releasing compound
Indication: Treat acne vulgaris
Endpoint: Absolute change from baseline in non-inflammatory lesion count at week 12; inflammatory lesion count and success on Investigator Global Assessment (IGA)
Status: Phase II data
Milestone: Additional Phase II data (2Q14); start clinical trial (3Q14)

A double-blind, international Phase II trial in 150 patients with acne showed that twice-daily topical SB204 1% and 4% gel each met the primary endpoint of reducing non-inflammatory lesion count from baseline to week 12 vs. vehicle control gel. SB204 4% gel also met the secondary endpoints of reducing inflammatory lesion count from baseline to week 12 and of improving the proportion of patients achieving a score of “clear” or “almost clear” and a 2-point improvement in IGA score at week 12 vs. vehicle-treated controls. SB204 1% gel missed the secondary endpoints. Additionally, SB204 4% gel significantly reduced both non-inflammatory and inflammatory lesion counts from baseline to week 4 vs. vehicle-treated controls (p<0.05). SB204 was tolerable with no serious adverse events reported. Novan plans to start a “late-stage clinical trial” with SB204 in 3Q14.

Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Product: Afinitor everolimus (Certican, Zortress, Votubia) (RAD001)
Business: Cancer
Molecular target: Mammalian target of rapamycin (mTOR) (FRAP) (RAFT1)
Description: Oral mTOR protein inhibitor
Indication: Treat estrogen receptor-positive, locally advanced or metastatic breast cancer
Endpoint: Progression-free survival (PFS); overall survival (OS), overall response rate (ORR), safety, patient reported outcomes and clinical benefit rate (CBR)
Status: Additional Phase III data
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Milestone: NA

Additional data from the double-blind, international Phase III BO-LERO-2 trial in 724 postmenopausal women with estrogen receptor-positive/HER2-negative, locally advanced or metastatic breast cancer showed that once-daily 10 mg oral Afinitor plus once-daily 25 mg exemestane missed the secondary endpoint of improving median OS vs. placebo plus exemestane (31 vs. 26.6 months, HR=0.89, 95% CI: 0.73, 1.1; p=0.1426). Data were presented at the European Breast Cancer meeting in Glasgow. Novartis previously reported that Afinitor plus exemestane met the primary endpoint of improving median PFS based on the local investigator’s radiology assessment vs. placebo plus exemestane (7.8 vs. 3.2 months, p<0.0001) (see BioCentury, July 11, 2011 & Oct. 3, 2011).

Novartis markets everolimus as Afinitor in the U.S. and EU to treat advanced renal cell carcinoma (RCC), breast cancer, neuroendocrine tumors of pancreatic origin and renal angiomyolipomas, as Certican to prevent renal and heart transplant rejection in over 90 countries, and as Zortress in the U.S. to prevent organ rejection of kidney and liver transplants. The drug was approved in Europe last year to prevent rejection of liver transplants. The product is also approved as Afinitor in the U.S. and as Votubia in the EU to treat subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) in patients who require therapeutic intervention but are not amenable to surgery. Pfizer Inc. (NYSE:PFE, New York, N.Y.) markets Aromasin to compete with exemestane.

Indication: Treat advanced solid tumors
Endpoint: Maximum tolerated dose (MTD) and safety; pharmacokinetics and objective response rate (ORR)
Status: Phase I data
Milestone: NA

Researchers at the Dana-Farber Cancer Institute and colleagues reported data from an open-label, U.S. Phase I trial in 9 patients with advanced solid tumors showing that pazopanib plus everolimus led to a complete response lasting for 14 months in 1 patient with bladder cancer plus 4 cases of stable disease — 3 patients with bladder cancer and 1 patient with adrenal gland cancer. Genomic profiling of the bladder cancer patient’s tumor identified 2 mutations — mTOR E2419K and mTOR E2014K. The researchers said the mutations likely rendered the patient’s cancer dependent on the mTOR pathway to survive and is likely the reason the cancer became sensitive to everolimus. Data were published in Cancer Discovery. The trial was funded by the Broad Institute, the National Human Genome Research Institute, GlaxoSmithKline plc (LSE:GSK; NYSE:GSK, London, U.K.) and Novartis. Novartis said it has no plans for additional studies with everolimus and pazopanib in bladder cancer, while GSK could not be reached for comment.

GlaxoSmithKline markets pazopanib, a broad-spectrum inhibitor of VEGF and other tyrosine kinases, as Votrient, and Novartis markets everolimus as Afinitor.

Product: Secukinumab (AIN457)
Business: Autoimmune
Molecular target: Interleukin-17A (IL-17A)
Description: Human IgG1 mAb targeting IL-17A
Indication: Treat moderate to severe plaque psoriasis
Endpoint: Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 and Investigator’s Global Assessment (IGA) responses at week 12; PASI 50/75/90/100, IGA 0/1, Self-Injection Assessment Questionnaire (SIAQ) scores and safety
Status: Phase III data
Milestone: NA

The double-blind, international Phase III JUNCTURE trial in 182 patients with moderate to severe plaque psoriasis showed that 150 and 300 mg subcutaneous secukinumab delivered via an autoinjector each met the co-primary endpoints of improving PASI 75 and IGA response rates at week 12 vs. placebo. Specifically, 71.7% of patients receiving low-dose secukinumab and 86.7% of patients receiving high-dose secukinumab achieved a PASI 75 response at week 12 vs. 3.3% for placebo (p<0.0001 for both). Additionally, 53.3% of patients receiving low-dose secukinumab and 73.3% of patients receiving high-dose secukinumab achieved an IGA response, defined as a score of 0 or 1 on a 5-point scale, at week 12 vs. 0% for placebo (p<0.0001).

Both doses of secukinumab also met all secondary endpoints vs. placebo. PASI 90 response rates at week 12 were 40% for low-dose secukinumab and 55% for high-dose secukinumab vs. 0% for placebo (p<0.0001 for both). Absolute mean SIAQ scores increased from baseline to week 12 by 1 point for feelings about self-injections, 1.47 points for self-confidence and 2.35 points for satisfaction across all groups. The most common adverse events reported were nasopharyngitis, headache and pruritus. The incidence of infections and infestations was higher in the secukinumab groups vs. placebo. No major safety signals were identified. Patients received 150 or 300 mg secukinumab or placebo at week 0, 1, 2 and 3, and then once every 4 weeks to week 48. At week 12, non-PASI 75 responders receiving placebo were re-randomized to 150 or 300 mg secukinumab once weekly until week 15 and then once every 4 weeks through week 48. Data were presented at the American Academy of Dermatology meeting in Denver.

Novartis previously reported that secukinumab met the co-primary endpoints of improving PASI 75 and IGA response rates at week 12 vs. placebo in the Phase III FIXTURE trial to treat moderate to severe chronic plaque psoriasis. Secukinumab also met the secondary endpoints of improving PASI 75 and IGA response rates at week 12 vs. Enbrel etanercept in FIXTURE (see BioCentury, July 15, 2013 & Oct. 21, 2013).

Last October, Novartis submitted regulatory applications in the U.S. and EU for secukinumab to treat moderate to severe plaque psoriasis. The pharma expects a decision from FDA and opinion from EMA’s CHMP on the applications next half. The product is also approved in Europe last year to prevent renal and heart transplant rejection in over 90 countries, and as Afinitor in Phase III trials of secukinumab in arthritic indications are expected in 2014. Agen Inc. (NASDAQ:AMGN, Thousand Oaks, Calif.) and Pfizer Inc. (NYSE:PFE, New York, N.Y.) co-market Enbrel in the U.S. and Canada, while Pfizer has rights elsewhere.

Indication: Treat moderate to severe chronic plaque-type psoriasis
Endpoint: Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 and Investigator’s Global Assessment (IGA) responses at week 12; PASI 50/75/90/100, IGA 0/1, Self-Injection Assessment Questionnaire (SIAQ) scores and safety
Status: Phase III data
Milestone: NA

The double-blind, international Phase III FEATURE trial in 177 patients with moderate to severe chronic plaque-type psoriasis showed that 150 and 300 mg subcutaneous secukinumab delivered via pre-filled syringes each met the co-primary endpoints of improving PASI 75 and IGA response rates at week 12 vs. placebo. Specifically, 69.5% of patients receiving low-dose secukinumab and 75.9% of patients receiving high-dose secukinumab achieved a PASI 75 response at week 12 vs. placebo.
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0% for placebo (p<0.0001 for both). Additionally, 52.5% of patients receiving low-dose secukinumab and 69% of patients receiving high-dose secukinumab achieved an IGA response, defined as a score of 0 or 1 on a 5-point scale, at week 12 vs. 0% for placebo (p<0.0001).

Both doses of secukinumab also met all secondary endpoints vs. placebo. PASI 90 response rates at week 12 were 27% for low-dose secukinumab and 59% for high-dose secukinumab vs. 0% for placebo (p<0.0001 for both). Overall mean SIQ scores increased from baseline to week 12 by 0.83 points for feelings about self-injections, 1.14 points for self-confidence and 1.52 points for satisfaction across all groups.

The most common adverse events reported were diarrhea, nasopharyngitis, headache and pyrexia, and the overall incidence of adverse events was similar across all treatment arms. Patients received 150 or 300 mg secukinumab or placebo at week 0, 1, 2, 3, 4 and 8, and then once every 4 weeks to week 48. At week 12, non-PASI 75 responders receiving placebo were re-randomized to 150 or 300 mg secukinumab once weekly until week 15 and then once every 4 weeks through week 48. Data were presented at the American Academy of Dermatology meeting in Denver.

Novartis previously reported that secukinumab met the co-primary endpoints of improving PASI 75 and IGA response rates at week 12 vs. placebo in the Phase III FIXTURE trial to treat moderate to severe chronic plaque psoriasis. Secukinumab also met the secondary endpoints of improving PASI 75 and IGA response rates at week 12 vs. Enbrel etanercept in FIXTURE (see BioCentury, July 15, 2013 & Oct. 21, 2013).

Last October, Novartis submitted regulatory applications in the U.S. and EU for secukinumab to treat moderate to severe plaque psoriasis. The pharma expects a decision from FDA and opinion from EMA’s CHMP on the applications next half. The product is also under postmarketing requirements for the accelerated approval.

Swedish Orphan Biovitrum AB (SSE:SOBI), Stockholm, Sweden Product: Kiobrina (BSSL) Business: Gastrointestinal Molecular target: Not applicable Description: Recombinant human bile salt-stimulated lipase (rhBSSL) Indication: Treat fat malabsorption in prematurely born infants Endpoint: Growth velocity from baseline to week 4; body weight, body length, head circumference, readiness for hospital discharge, Neurodevelopment Disability Composite and safety Status: Phase III data Milestone: Additional Phase III data (year end 2014)

Top-line data from the double-blind, European Phase III LAIF study in 410 preterm infants <32 weeks of gestational age showed that Kiobrina added to preterm formula or pasteurized breast milk missed the primary endpoint of improving median growth velocity from baseline to week 4 vs. placebo added to preterm formula or pasteurized breast milk (16.8 vs. 16.6 g/kg/day, p=0.49). Kiobrina also missed the secondary endpoints of improving head circumference (3.92 vs. 3.88 cm, p=0.06).
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p=0.66) and readiness for hospital discharge (45.1 vs. 45.2 days, p=0.93) vs. placebo.

In a pre-specified subgroup of infants small for gestational age (n=62), which are infants with a birth weight below the 10th percentile for gestational age, Kiobrina improved mean growth velocity by 17.1 g/kg/day from baseline to week 4 vs. 15.1 g/kg/day placebo. Swedish Orphan said further analysis is required to determine the relevance of the small for gestational age finding. There was a higher incidence of adverse events observed in the Kiobrina arm vs. the placebo arm. In the Kiobrina arm, there were signs of gastrointestinal intolerance and potential cases of necrotizing enterocolitis.

Based on the results, Swedish Orphan said it will not start a U.S. Phase III trial of Kiobrina in the indication, which was slated to start in 2Q14. The company expects additional data from the LAIF trial, including fatty acid profiles and neurocognitive assessments, by year end and said a decision regarding next steps for Kiobrina will be made once all of the data are analyzed.

**Synta Pharmaceuticals Corp.** (NASDAQ:SNTA), Lexington, Mass.

**Product:** Ganetespib (formerly STA-9090)

**Business:** Cancer

**Molecular target:** Heat shock protein 90 (Hsp90)

**Description:** Small molecule heat shock protein 90 (Hsp90) inhibitor

**Indication:** First-line treatment of metastatic HER2-positive, estrogen receptor/progesterone receptor (ER/PR)-positive or triple negative breast cancer (TNBC)

**Endpoint:** Overall response rate (ORR) at week 12; metabolic response, duration of response, progression-free survival (PFS) and biomarkers

**Status:** Additional Phase II data

**Milestone:** NA

Additional data from the 2-stage, open-label, international Phase II ENCHANT-1 trial showed that twice-weekly IV 150 mg/m² ganetespib as monotherapy for 3 weeks of a 4-week cycle led to 4 objective responses, including 1 complete response, and 2 cases of stable disease at week 6 in 6 evaluable patients with newly diagnosed locally advanced or metastatic HER2-positive breast cancer. In 26 evaluable patients with TNBC, ganetespib led to 2 objective responses and 11 cases of stable disease at week 6. Additionally, of 7 evaluable HER2-positive patients, 6 achieved metabolic responses based on comparing PET scans from baseline to week 3. Of 31 evaluable TNBC patients, 18 achieved a metabolic response. Data were presented at the European Breast Cancer meeting in Glasgow.

Last year, Synta reported that ganetespib met the pre-specified criterion for advancing to stage 2 of the trial in both the HER2-positive and TNBC cohorts. To advance to stage 2 of the trial, each cohort required ≥1 objective tumor response out of the first 15 evaluable patients (see BioCentury, Aug. 5, 2013). In stage 2, each cohort will enroll up to 35 patients. The company has also added a third cohort of ER/PR-positive patients previously untreated for locally advanced or metastatic breast cancer. At week 6, patients with progressive disease are eligible to receive ganetespib in combination with weekly paclitaxel and patients with a response or stable disease can continue ganetespib as monotherapy until disease progression.

Earlier this month, the non-profit Quantum Leap Healthcare Collaborative said ganetespib was selected to join the open-label Phase II I-SPY 2 trial. The trial is designed to rapidly and inexpensively develop data to support small Phase III trials of new neoadjuvant therapies for locally advanced breast cancer or to help companies quickly kill ineffective candidates. I-SPY 2 involves an adaptive trial design based on Bayesian predictive probability that a regimen will be statistically superior to standard therapy in an equally randomized 300-patient confirmatory trial. Investigators will initially use ganetespib in HER2-negative patients, and then expand use to include all breast cancer subtypes, including HER2-positive disease. Enrollment in the ganetespib arm for I-SPY 2 is slated to start this year (see BioCentury, March 17).

Ganetespib also is in the Phase III GALAXY-2 trial to treat non-small cell lung cancer (NSCLC). Ganetespib has Fast Track designation in the U.S. as second-line treatment of NSCLC.

**Synthon B.V., Nijmegen, the Netherlands**

**Product:** Generic glatiramer acetate

**Business:** Autoimmune

**Molecular target:** Major histocompatibility complex class II (MHCII)

**Description:** Generic version of Copaxone glatiramer acetate, a selective major histocompatibility complex (MHCII) class II modulator

**Indication:** Treat relapsing-remitting multiple sclerosis (RRMS)

**Endpoint:** Number of T1 gadolinium-enhancing brain lesions as measured by MRI scans from baseline at 7, 8 and 9 months; incidence of MS relapses, disability, patient-reported tolerability and safety

**Status:** Phase III data

**Milestone:** NA

The double-blind, international Phase III GATE trial in 796 patients with active RRMS showed that once-daily 20 mg/mL injections of Synthon’s generic glatiramer acetate for 9 months met the primary endpoint of equivalence to Copaxone glatiramer acetate in reducing the number of T1 gadolinium-enhancing brain lesions as measured by MRI scans from baseline at 7, 8 and 9 months. Both Synthon’s generic glatiramer acetate and Copaxone led to significant reductions on the endpoint vs. placebo. Synthon also said that other outcomes, including the incidence of MS relapses, disability and patient-reported tolerability, support the primary outcome. The incidence of adverse events was comparable between glatiramer acetate treatment arms. The trial also includes an open-label extension in which all patients, including patients who received Copaxone or placebo in the double-blind portion, will receive generic glatiramer acetate for an additional 15 months.

Synthon plans to submit a regulatory application in Europe for generic glatiramer acetate, but could not be reached for a time frame. The company submitted an ANDA to FDA for the generic in 2011 (see BioCentury, Dec. 19, 2011). In 2012, Teva Pharmaceutical Industries Ltd. (NYSE:TEVA, Petah Tikva, Israel) filed suit in the U.S. District Court for the Southern District of New York and the U.S. District Court for the Eastern District of North Carolina Western District claiming that the ANDA infringes Teva’s patents covering Copaxone (see BioCentury, April 16, 2012). Teva markets Copaxone in the U.S. and shares European rights with Sanofi (Euronext:SAN;NYSE:SNY, Paris, France). Teva, which loses U.S. exclusivity for Copaxone on May 24, reported $4.3 billion in 2013 sales for the product.

**VolutionRx Ltd.** (OTCBB:VNRX), Singapore

**Product:** NuQ tests

**Business:** Diagnostic

**Molecular target:** NA

**Description:** Family of non-invasive blood tests for nucleosomes

**Indication:** Detect prostate cancer

**Endpoint:** Sensitivity and specificity

**Status:** Pilot trial data

**Milestone:** NA

Data from 9 males with newly diagnosed prostate cancer and 10 healthy controls in a pilot trial showed that VolutionRx’s NuQ tests for circulating nucleosomes containing methylated DNA or histone modifications had 80% sensitivity and 70% specificity for detecting prostate
cancer. Data were presented at the International Society of Oncology and Biomarkers meeting in Barcelona.

Last December, VolitionRx reported data from 39 subjects referred for colonoscopy in a prospective Belgian trial showing that the NuQ tests had 85% sensitivity and 85% specificity for detecting colorectal cancer (see BioCentury, Jan. 27). The tests are based on VolitionRx’s Nucleosomes biomarker development platform, which identifies and measures nucleosome structures in cell culture, serum, plasma or other biofluids. NuQ tests are available worldwide for research-use only.

**PRECLINICAL RESULTS**

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

**Product:** Trilexium (Trx-1)

**Business:** Cancer

**Indication:** Treat ovarian cancer

In a mouse xenograft model of ovarian cancer, Trx-1 significantly reduced tumor growth. Last November, 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. Under the deal, CanTx will assume responsibility for development of Novogen’s super-benzopyran drug technology to treat ovarian cancer and will license a drug delivery system from the university. CanTx, which has exclusive, worldwide rights to develop Trx-1 from Novogen, plans to start a Phase I trial with the super-benzopyran compound to treat ovarian cancer in IH15 (see BioCentury, Nov. 11, 2013).

**CLINICAL STATUS**

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

**Eisai Co. Ltd.** (Tokyo:4523), Tokyo, Japan

**Product:** Humira adalimumab

**Business:** Autoimmune

**Molecular target:** Tumor necrosis factor (TNF) alpha

**Description:** Human mAb against tumor necrosis factor (TNF) alpha

**Indication:** Treat fingernail psoriasis in patients with moderate to severe chronic plaque psoriasis

**Endpoint:** Proportion of patients achieving a total-fingernail modified Nail Psoriasis Severity Index (mNAPSI) 75 response and Physician’s Global Assessment of Fingernails of “clear” or “minimal” at week 26; percent change in mNAPSI, Nail Psoriasis Pain Numeric Rating Scale (NRS), Nail Psoriasis Physical Functioning Severity Score and Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index (B-SNIPI)

**Status:** Phase III started

**Milestone:** NA

AbbVie began a double-blind, placebo-controlled, international Phase III trial to evaluate subcutaneous Humira given every other week for 26 weeks in about 200 adults with moderate to severe chronic plaque psoriasis and ≥1 fingernail with nail psoriasis. Humira is approved in the U.S. and EU to treat adults with moderately to severely active Crohn’s disease (CD), moderate to severe rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, chronic plaque psoriasis and ulcerative colitis (UC) and to treat polyarticular juvenile idiopathic arthritis in patients ≥4 years old.

Eisai and Abbott Laboratories (NYSE:ABT, Abbott Park, Ill.) jointly developed Humira and co-promote it in Japan, Korea and Taiwan. Abbott has rights to the product elsewhere. Abbott spun out its pharmaceuticals business into AbbVie in January 2013.

**Agios Pharmaceuticals Inc.** (NASDAQ:AGIO), Cambridge, Mass.

**Product:** IDH1 inhibitor (AG-120)

**Business:** Cancer

**Molecular target:** Isocitrate dehydrogenase 1 (IDH1)

**Description:** Inhibitor of mutated isocitrate dehydrogenase 1 (IDH1)

**Indication:** Treat advanced hematologic malignancies

**Endpoint:** Safety, maximum tolerated dose (MTD) and recommended Phase II dose; pharmacokinetics and clinical activity according to 2006 modified International Working Group (IWG) criteria

**Status:** Phase I started

Agios began an open-label, dose-escalation, international Phase I trial to evaluate oral AG-120 daily in 28-day cycles in about 50 patients with advanced hematologic malignancies that have an IDH1 mutation, including acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). The product is also in Phase I testing for solid tumors that have an IDH1 mutation.

Last month, Agios exercised its option under a 2010 cancer metabolism deal with Celgene Corp. (NASDAQ:CELG, Summit, N.J.) to retain U.S. development and commercialization rights to the IDH1 program, including AG-120. Celgene retains the option to license ex-U.S. development and commercialization rights to AG-120 at the end of Phase I testing (see BioCentury, Feb. 10).

**Alkermes plc** (NASDAQ:ALKS), Dublin, Ireland

**Product:** ALKS 5461

**Business:** Neurology

**Molecular target:** Mu opioid receptor (OPRM1) (MOR); Kappa opioid receptor (OPRK1) (KOR)

**Description:** Combination of ALKS 33, a mu opioid receptor (OPRM1; MOR) antagonist, and buprenorphine

**Indication:** Treat refractory major depressive disorder (MDD)

**Endpoint:** Safety

**Status:** Phase III started

**Milestone:** Start Phase III (mid-2014)

Alkermes began a double-blind, U.S. Phase III trial to evaluate 2 titration schedules of once-daily oral ALKS 5461 in about 60 patients with MDD who had an inadequate response to antidepressant therapy. The trial is the first in Alkermes’ Phase III FORWARD program for the adjunctive treatment of MDD, which consists of 12 studies, including 3 “core” studies slated to start in mid-2014 in about 1,500 MDD patients who have had an inadequate response to standard therapies. The primary endpoint in the core studies will be the change in Montgomery-Asberg Depression Rating Scale (MADRS) scores. The remaining 9...
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trials will evaluate long-term safety, dosing, pharmacokinetics and human abuse liability of ALKS 5461. ALKS 5461 has Fast Track designation in the U.S. for adjunctive treatment of MDD in patients with an inadequate response to standard therapies.

Antisense Therapeutics Ltd. (ASX:ANP), Toorak, Australia
Isis Pharmaceuticals Inc. (NASDAQ:ISIS), Carlsbad, Calif.
Product: ATL1103
Business: Endocrine/Metabolic
Molecular target: Growth hormone receptor
Description: Second-generation antisense inhibitor of growth hormone receptor expression
Indication: Treat acromegaly
Endpoint: Safety and pharmacokinetics; percent change from baseline in serum insulin-like growth factor-1 (IGF-1) levels at week 14 and pharmacodynamics
Status: Completed Phase II enrollment
Milestone: Phase II data (mid-2014)

Antisense completed enrollment of 24 acromegalic patients in an open-label, European and Australian Phase II trial evaluating 3 doses of 200 mg ATL1103 in the first week of treatment, followed by once- or twice-weekly 200 mg ATL1103 for 12 weeks. In January, the company reported interim data from the first 8 patients in the trial showing that ATL1103 was well tolerated (see BioCentury, Jan. 27). Antisense in-licensed ATL1103 from Isis, which is eligible for royalties.

Product: ATL1102, ISIS 107248 (formerly ATL-TV-1102)
Business: Endocrine/Metabolic
Molecular target: Integrin alpha(4) (VLA-4) (CD49D) mRNA
Description: Second-generation antisense oligonucleotide (ASO) targeting VLA-4 mRNA
Indication: Mobilization agent for stem cell transplantation
Endpoint: Safety and pharmacokinetics
Status: Phase I started
Milestone: Phase I data (mid-2014)

Antisense began an open-label, Australian Phase I trial to evaluate 400 mg subcutaneous ATL1102 on days 1, 3 and 5 with or without G-CSF for 5 days in 10 healthy volunteers. Antisense has rights to ATL1102 from Isis (see BioCentury, July 23, 2012).

Ariad Pharmaceuticals Inc. (NASDAQ:ARIA), Cambridge, Mass.
Product: AP26113
Business: Cancer
Molecular target: Anaplastic lymphoma kinase (ALK); Epidermal growth factor receptor (EGFR)
Description: Dual inhibitor of anaplastic lymphoma kinase (ALK) and EGFR
Indication: Treat ALK-positive non-small cell lung cancer (NSCLC)
Endpoint: Objective response rate (ORR); time to response, duration of response, disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety
Status: Phase II started
Milestone: Complete Phase II enrollment (3Q15); Phase II data (2015)

Ariad began the open-label, international, pivotal Phase II ALTA trial to evaluate oral AP26113 in about 220 patients with ALK-positive NSCLC who progressed after treatment with crizotinib. Patients will receive either 90 mg AP26113 once daily or a lead-in dose of 90 mg AP26113 once daily for 7 days followed by 180 mg AP26113 once daily thereafter. Pfizer Inc. (NYSE:PFE, New York, N.Y.) markets Xalkori crizotinib.

BioMarin Pharmaceutical Inc. (NASDAQ:MRNR), Novato, Calif.
Catalyst Pharmaceutical Partners Inc. (NASDAQ:CPRX), Coral Gables, Fla.
Jazz Pharmaceuticals plc (NASDAQ:JAZZ), Dublin, Ireland
Product: Firdapse amifampridine
Business: Autoimmune
Molecular target: Potassium channel
Description: Potassium channel blocker
Indication: Treat Lambert-Eaton myasthenic syndrome (LEMS)
Endpoint: Quantitative myasthenia gravis score; timed 25-foot walk test
Status: Phase III ongoing
Milestone: Complete Phase III enrollment (I Q14); Phase III data (3Q14); complete rolling NDA (mid-2015)

Catalyst said an IDMC recommended continuation of a double-blind, placebo-controlled, international Phase III trial of Firdapse based on a review of safety and clinical data. The trial is evaluating Firdapse given 3-4 times daily in about 36 patients, who will receive a total daily dose of 30-80 mg, except in patients with moderate renal impairment, who will receive a starting dose of 10 mg.

In 2012, BioMarin granted Catalyst exclusive, North American rights to Firdapse (see BioCentury, Nov. 5, 2012). The product is approved for LEMS in the EU, where it has Orphan Drug status. Firdapse has breakthrough therapy designation in the U.S. and Orphan Drug designation in the U.S. and Switzerland. BioMarin gained the compound through its 2009 acquisition of Huxley Pharmaceuticals Inc. which licensed it from EUSA Pharma Inc. Jazz acquired EUSA Pharma in 2012 (see BioCentury, Nov. 2, 2009 & June 18, 2012). LEMS is a rare disorder of neuromuscular transmission caused by impaired presynaptic release of acetylcholine.

bluebird bio Inc. (NASDAQ:BLUE), Cambridge, Mass.
Product: LentiGlobin gene therapy (BB305)
Business: Hematology
Molecular target: NA
Description: Lentiviral vector encoding the human beta globin gene delivered into a patient’s own hematopoietic stem cells in the bone marrow
Indication: Treat beta thalassemia major
Endpoint: Production of hemoglobin containing the therapeutic globin protein and safety; hematopoietic stem cell engraftment and transgene marking as measured by the average vector copy number in peripheral blood and bone marrow
Status: Phase I/II started
Milestone: NA

bluebird bio began the open-label, U.S. Phase I/II Northstar (HGB-204) trial to evaluate LentiGlobin gene therapy in up to 15 patients with beta thalassemia major undergoing autologous hematopoietic stem cell transplantation (HSCT). LentiGlobin is also being evaluated in the French Phase I/II HGB-205 trial in patients with beta thalassemia major and severe sickle cell disease undergoing autologous HSCT.

Product: MVA-EBNA/LMP2 vaccine
Business: Cancer
Molecular target: NA
Description: Vaccine consisting of a recombinant modified vaccinia Ankara (MVA) viral vector encoding the gene for the Epstein-Barr virus (EBV) antigen Epstein-Barr nuclear antigen 1 (EBNA1) and fused to the EBV-associated antigen latent membrane protein 2
Indication: Treat EBV-positive nasopharyngeal carcinoma
Endpoint: Immune response and safety; immune memory and recall

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- **Response, EBV genome levels and tumor response**
- **Status: Phase Ib started**
- **Milestone: NA**

Cancer Research UK said its Drug Development Office (DDO) began a U.K. Phase Ib trial to evaluate 3 doses of intradermal MVAE2NA-EBNA-LMP2 vaccine every 3 weeks followed by another dose 12 weeks later in 18 patients with EPV-positive nasopharyngeal carcinoma. The vaccine has been developed by Cancer Research UK with technology developed by the University of Birmingham (Birmingham, U.K.). Cancer Research UK is funding the trial and its DDO owns and is supplying the vaccine for the trial. The vaccine is also in a Hong Kong Phase II trial.

**Celator Pharmaceuticals Inc.** (NASDAQ:CPXX), Ewing, N.J.

- **Product:** CPX-351
- **Business:** Cancer
- **Molecular target:** DNA polymerase; Topoisomerase II (TOP2)
- **Description:** Liposomal formulation of cytarabine and daunorubicin encapsulated at a 5:1 molar ratio using CombiPlex technology
- **Indication:** Treat relapsed or refractory high-risk myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML)
- **Endpoint:** Safety and response rate at day 42; duration of remission, overall survival (OS) at 12 months and early mortality within the first 60 days of first induction
- **Status:** Phase II started
- **Milestone: NA**

Celator said investigators began an open-label, U.S. Phase II trial to evaluate IV CPX-351 in up to 33 patients ages ≥60 years with higher risk MDS or AML who are refractory or relapsed after hypomethylating agent therapy. Patients will receive induction therapy with CPX-351 on days 1, 3 and 5, with a second induction therapy on days 1 and 3 if a morphological leukemia-free state is not achieved. Those that achieve complete remission after 1-2 inductions will receive consolidation therapy with CPX-351 on days 1 and 3.

CPX-351 is also in Phase III testing for first-line treatment of high-risk AML. The compound has Orphan Drug designation in the U.S. and EU to treat AML.

**Cortice Biosciences Inc.,** New York, N.Y.

- **Product:** TPI 287
- **Business:** Cancer
- **Molecular target:** Not available
- **Description:** Third-generation taxane
- **Indication:** Treat glioblastoma multiforme (GBM)
- **Endpoint:** Safety and maximum tolerated dose (MTD); progression-free survival (PFS) and overall response rate (ORR)
- **Status:** Phase II started
- **Milestone: NA**

Cortice began a 2-stage, open-label, dose-escalation, U.S. Phase II trial of IV TPI 287 every 3 weeks plus 10 mg/m² IV Avastin bevacizumab every 2 weeks in 6-week cycles in about 18 patients with recurrent GBM who progressed following prior following prior treatment with radiation, temozolomide and Avastin. The first stage will determine the MTD of TPI 287 plus Avastin. Once the MTD for TPI 287 is established, patients will receive Avastin alone or in combination with TPI 287 in the expansion stage. Genentech Inc., a unit of Roche (SIX:ROG; OTCQX:RHHBY, Basel, Switzerland), markets Avastin in the U.S., while Roche markets it elsewhere.

**BioCentury Extra:** Online every business day.

- **CymaBay Therapeutics Inc.** (OTCBB:CYMA), Newark, Calif.
  - **Product:** Arhalofenate (MBX-102)
  - **Business:** Endocrine/Metabolic
  - **Molecular target:** Solute carrier family 22 organic anion urate transporter member 12 (SLC22A12) (URAT1)
  - **Description:** Uricosuric agent
  - **Indication:** Treat gout
  - **Endpoint:** Flare incidence rate at 12 weeks; serum uric acid responder rate, defined as serum uric acid levels of <6 mg/dL
  - **Status:** Phase Ib started
  - **Milestone: NA**

CymaBay began a double-blind, placebo-controlled Phase Ib trial to compare 600 and 800 mg oral arhalofenate once daily vs. 300 mg oral allopurinol once daily with or without 0.6 mg oral colchicine once daily for 12 weeks in about 225 patients with gout, hyperuricemia and a history of ≥3 flares in the last 12 months.

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

- **Astellas Pharma Inc.** (Tokyo:4503), Tokyo, Japan
  - **Product:** CK-2127107
  - **Business:** Musculoskeletal
  - **Molecular target:** Sarcomere
  - **Description:** Fast skeletal muscle troponin activator
  - **Indication:** Treat neuromuscular dysfunction, muscular weakness and muscle fatigue
  - **Endpoint:** Safety and pharmacokinetics
  - **Status:** Phase I started
  - **Milestone: NA**

Cytokinetics began the double-blind, placebo-controlled, dose-escalation Phase I CY 5012 trial to evaluate oral CK-2127107 given for 10 days in healthy volunteers ages 18-35 and 65-85 years. Subjects in both age groups will receive 300 and 1,000 mg doses, while subjects ages 18-55 years may also receive 1,500 and 2,000 mg doses. The trial start triggered a $2 million milestone payment to Cytokinetics from Astellas. Last June, Cytokinetics and Astellas partnered to develop and commercialize skeletal muscle activators to treat diseases and conditions with muscle weakness in a deal worth up to $490 million (see BioCentury, July 1, 2013).

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

- **Product:** Cytori Cell Therapy, adipose-derived regenerative cells (ADRCs)
  - **Business:** Musculoskeletal
  - **Molecular target:** Not available
  - **Description:** Adipose-derived regenerative cells (ADRCs)
  - **Indication:** Treat anterior cruciate ligament (ACL) injury
  - **Endpoint:** NA
  - **Status:** Phase II started
  - **Milestone: Complete Phase II enrollment (2014)**

Cytori said last year investigators began an open-label, Spanish Phase II trial to evaluate Cytori Cell Therapy in about 20 patients undergoing complete ACL reconstruction for sports-related injuries. Cytori Cell Therapy is also in the open-label, U.S. Phase II RECOVER trial to treat hamstring injuries. Cytori Cell Therapy is derived from the company’s Celution System, a device used to process and purify adult stem and regenerative cells from adipose tissue.

**CytRx Corp.** (NASDAQ:CYTR), Los Angeles, Calif.

- **Product:** Aldoxorubicin (formerly DOXO-EMCH, INNO-206)
  - **Business:** Cancer

CytRx owns and is supplying the vaccine for the trial. The vaccine has been developed by Cancer Research UK with technology developed by the University of Birmingham (Birmingham, U.K.). Cancer Research UK is funding the trial and its DDO owns and is supplying the vaccine for the trial. The vaccine is also in a Hong Kong Phase II trial.
Molecular target: DNA
Description: 6-maleimidocaproyl hydrazone prodrug of doxorubicin
Indication: Treat soft tissue sarcoma (STS)
Endpoint: Progression-free survival (PFS); overall survival (OS), overall response rate (ORR) and safety
Status: Phase III started
Milestone: Complete Phase III enrollment (2015)

CytRx began an open-label, international Phase III trial to compare 350 mg/m² IV doxorubicin on day 1 of every 21-day cycle vs. investigator’s choice of an approved chemotherapeutic regimen in about 400 patients. The company has an SPA from FDA for the trial, which plans to enroll patients with metastatic, locally advanced or unresectable STS who have either not responded to or have progressed following treatment with ≥1 systemic regimen of non-adjuvant chemotherapy.

Aldoxorubicin is also in Phase II testing for glioblastoma multiforme (GBM) and AIDS-related Kaposi’s sarcoma. The compound has Orphan Drug designation in the U.S. for STS and pancreatic cancer. Last year, CytRx said that it terminated for lack of efficacy a Phase II trial with aldoxorubicin as a third-line treatment of advanced pancreatic ductal adenocarcinomas. CytRx said it has no plans to further develop the compound for pancreatic cancer.

**e-Therapeutics plc** (LSE:ETX), Newcastle upon Tyne, U.K.
Product: Dexanabinol (ETS2101)
Business: Cancer
Molecular target: Not available
Description: Small molecule chemotherapeutic synthetic cannabinoid
Indication: Treat advanced solid tumors
Endpoint: Safety and maximum tolerated dose (MTD); pharmacokinetics and tumor response
Status: Phase I ongoing
Milestone: Final Phase I data (1Q14)

e-Therapeutics said it received approval from the U.K.’s Medicines and Healthcare products Regulatory Agency (MHRA) to resume enrollment in an open-label, dose-escalation, U.K. Phase I trial evaluating IV ETS2101 on days 1, 8 and 15 of a 21-day cycle in up to 45 patients with advanced solid tumors. The company said an investigator-led, U.S. Phase I trial in primary or secondary brain cancer has not yet received approval to resume enrollment. In January, e-Therapeutics halted enrollment in the trials due to a “practical issue with stored drug” for the trials (see BioCentury, Jan. 27).

**Exelixis Inc.** (NASDAQ:EXEL), South San Francisco, Calif.
Product: Cometriq cabozantinib (XL184)
Business: Cancer
Molecular target: Vascular endothelial growth factor (VEGF) receptor 2 (KDR/Flk-1) (VEGFR-2); c-Met receptor tyrosine kinase
Description: Spectrum-selective kinase inhibitor of VEGF receptor 2 (KDR/Flk-1) (VEGFR-2) and c-Met receptor tyrosine kinase
Indication: Treat metastatic castration-resistant prostate cancer (CRPC)
Endpoint: Overall survival (OS); bone scan response
Status: Phase III ongoing
Milestone: Phase III data (2014)

An IDMC said that the double-blind, placebo-controlled, international Phase III COMET-1 trial evaluating Cometriq did not meet criteria to support early trial unblinding. The IDMC recommended continuing the trial based on a planned interim analysis of the primary OS endpoint. A final analysis is scheduled when there are 578 events, with data expected this year. COMET-1 enrolled 960 patients and is comparing Cometriq vs. prednisone in patients who have progressed following treatment with docetaxel and Zytiga abiraterone or Xtandi enzalutamide.

Exelixis markets Cometriq in the U.S. to treat progressive, metastatic medullary thyroid cancer (MTC). Last week, the European Commission conditionally approved the drug to treat progressive, unresectable, locally advanced or metastatic MTC. The drug has Orphan Drug status in the EU for MTC. The product is also in 4 other Phase III trials: the COMET-2 trial to treat CRPC in patients who suffer from moderate to severe bone pain despite optimized narcotic medication; the METEOR trial to treat metastatic renal cell carcinoma (RCC); the EXAM trial to treat MTC; and the CELESTIAL trial to treat hepatocellular carcinoma (HCC). The product is also in a Phase II trial in chemotherapy-naïve patients with CRPC who have bone metastases.


**Fate Therapeutics Inc.** (NASDAQ:FATE), San Diego, Calif.
Product: ProHema
Business: Cancer
Molecular target: NA
Description: Hematopoietic stem cells modulated with FT1050, a small molecule prostaglandin E2 analog
Indication: Treat hematologic malignancies
Endpoint: Cumulative incidence of time to neutrophil engraftment; neutrophil and platelet engraftment, graft failure, acute graft-versus-host disease (GvHD), serious infection, disease-free survival and overall survival (OS)
Status: Phase II started
Milestone: Interim Phase II data (2H14); additional Phase II data (mid-2015)

Fate began the open-label, U.S. Phase II PUMA trial to compare a nutrient-rich media formulation of ProHema plus an unmanipulated cord blood unit vs. 2 unmanipulated cord blood units in 60 patients ages 15-65 years with hematologic malignancies who are undergoing hematopoietic stem cell transplantation (HSCT). Fate expects interim data next half and full data on the primary endpoint in mid-2015.

Last August, Fate disclosed in an S-1 filing that it paused enrollment in a Phase II trial with ProHema, with plans to resume the trial this year with an “improved nutrient-rich media formulation” of ProHema (see BioCentury, Aug. 19, 2013). Fate could not be reached on whether PUMA and the paused trial are the same trial. Fate said that ProHema manufactured using the nutrient-rich media formulation showed a more than 2-fold improvement in engraftment in preclinical studies vs. the prior formulation.

**FibroGen Inc.**, San Francisco, Calif.
**Astellas Pharma Inc.** (Tokyo:4503), Tokyo, Japan
**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.
Product: Roxadustat (FG-4592, ASPI1517)
Business: Hematology
Molecular target: Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) (EGLN)
Description: Small molecule inhibitor of hypoxia-inducible factor prolyl hydroxylase (HIF-PH; EGLN)

See next page
Clinical Status, from previous page

Indication: Treat anemia in chronic kidney disease (CKD) patients
Endpoint: Hemoglobin response; hemoglobin maintenance, LDL-C, SF-36 Physical Functioning subscore, SF-36 Vitality subscore, blood pressure, rescue therapy and safety
Status: Phase III started
Milestone: Start Phase III (1H14); start Phase III (09/2014); complete Phase III (year end 2016)

Astellas began the double-blind, placebo-controlled, international Phase III ALPS trial to evaluate oral roxadustat in about 600 CKD patients not requiring dialysis. Patients will receive roxadustat thrice weekly during the correction period followed by weekly, twice-weekly or thrice-weekly during the maintenance period. The trial is part of the Phase III ALPINE program in 1,800 patients in Europe, which includes the Phase III DOLOMITE trial expected to start by April, and the Phase III PYRENEES trial expected to start in September.

Astellas has rights to roxadustat from FibroGen in Japan, Europe, the Commonwealth of Independent States (CIS), the Middle East and South Africa. Last year, FibroGen and AstraZeneca partnered to develop and commercialize roxadustat worldwide, excluding the countries in which Astellas already has rights (see BioCentury, May 1, 2006 & Aug. 5, 2013).

Hua Medicine Ltd., Shanghai, China
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

Product: HMS5552, ROS305552
Business: Endocrine/Metabolic
Molecular target: Glucokinase (GCK) (GK)
Description: Small molecule glucokinase (GCK; GK) activator
Indication: Treat Type II diabetes
Endpoint: Safety; pharmacokinetics
Status: Phase Ib started
Milestone: Complete Phase Ib (3Q14)

Hua Medicine began a double-blind, placebo-controlled Phase Ib trial to evaluate multiple ascending-doses of 25-400 mg oral HMS5552 twice daily in about 50 patients. Hua Medicine has exclusive, worldwide rights to develop and commercialize Roche’s GCK activator program, including HMS5552, under a 2011 deal (see BioCentury, Jan. 2, 2012).

Kamada Ltd. (Tel Aviv:KMDA; NASDAQ:KMDA), Ness Ziona, Israel
Pari GmbH, Starnberg, Germany

Product: Aerosolized Alpha-1 antitrypsin (AAT) (AAT-IH)
Business: Endocrine/Metabolic
Molecular target: NA
Description: Aerosolized alpha-1 proteinase inhibitor (API)
Indication: Treat alpha-1 antitrypsin deficiency
Endpoint: Concentration of active AAT in epithelial lining fluid (ELF); safety, concentration of active AAT in serum and ELF inflammatory analytes
Status: Phase II started
Milestone: Phase II/I/III data (2Q14); submit MAA (2H14)

Kamada began a double-blind, placebo-controlled, U.S. Phase II trial to evaluate 80 or 160 mg inhaled AAT twice daily for 12 weeks in 36 patients. Patients will be eligible to enroll in a 12-week, open-label extension study. The product, which uses the eFlow Nebulizer System from Pari, completed a European and Canadian Phase II/III trial to treat AAT deficiency, with top-line data expected by the end of April or the start of May and an MAA submission to EMA expected next half.

Next half, Kamada plans to start a Phase II trial with AAT to treat cystic fibrosis (CF). The product has Orphan Drug designation in the U.S. and EU for CF and AAT deficiency and in the U.S. to treat bronchiectasis.

Kinex Pharmaceuticals LLC, Buffalo, N.Y.
PharmaEssentia Corp., Taipei, Taiwan
Hanmi Pharmaceutical Co. Ltd. (KOSDAQ:128940), Seoul, South Korea
Product: Oraxol
Business: Cancer
Molecular target: P glycoprotein (MDR1) (ABCBI) (P-gp) (CD243)
Description: Oral formulation of paclitaxel and HM30181A, a P glycoprotein (MDR1; ABCBI; P-gp; CD243) inhibitor
Indication: Treat cancer
Endpoint: Bioavailability
Status: Phase I start
Milestone: Start Phase I (04/2014)

Next month, Kinex and partner Zenith Technology Ltd. (Dunedin, New Zealand) will begin an open-label, crossover, New Zealand Phase I trial to compare 270 mg oral Oraxol vs. IV paclitaxel in 8 cancer patients. Kinex plans to pursue development of Oraxol under section 505(b)(2) of the Food, Drug and Cosmetic Act, which allows sponsors to reference data on safety and efficacy from scientific literature or from previously approved products. Kinex has exclusive rights from Hanmi under a December 2011 deal to develop and commercialize Hanmi’s Orascovery drug delivery technology, which includes Oraxol. Zenith has marketing rights from Kinex to Oraxol in New Zealand and Australia under a 2013 deal (see BioCentury, May 13, 2013). PharmaEssentia has exclusive development and commercialization rights from Kinex to Oraxol in Taiwan and Singapore (see BioCentury, Feb. 17).

Mast Therapeutics Inc. (NYSE-M:MSTX), San Diego, Calif.
Product: Purified poloxamer 188 (MST-188) (formerly ANX-188)
Business: Cardiovascular
Molecular target: NA
Description: Anti-thrombotic poloxamer that binds to hydrophobic surfaces on damaged cells
Indication: Treat acute lower limb ischemia
Endpoint: Angiographic assessment of the change in the volume of thrombus, change in transcutaneous oxygen tension (TcPO2) and safety
Status: Phase II started
Milestone: Complete Phase II enrollment (2H15)

Mast began a double-blind, placebo-controlled, international Phase II trial to evaluate a low and high dose of IV MST-188 in about 60 patients with acute lower limb ischemia receiving catheter-directed recombiant tissue plasminogen activator (tPA). Patients in the low-dose arm will receive a loading dose of 100 mg/kg MST-188 for 1 hour followed by 25 mg/kg/hour MST-188 for 11 hours, and those in the high-dose arm will receive a loading dose of 200 mg/kg MST-188 for 1 hour followed by 75 mg/kg/hour MST-188 for 11 hours. MST-188 has Orphan Drug designation in the U.S. and EU to treat acute limb ischemia and sickle cell disease, for which it is in Phase III testing.

Merck KGaA (Xetra:MRK), Darmstadt, Germany
Product: Pergoveris follitropin alfa/lutropin alfa
Business: Endocrine/Metabolic
Molecular target: Follicle stimulating hormone (FSH) receptor
Description: Fixed dose combination of follitropin alfa, a recombinant human follicle stimulating hormone (r-hFSH), and lutropin alfa, a recombinant human luteinizing hormone (r-hLH)
Indication: Stimulation multifollicular development
Endpoint: Total number of retrieved oocytes; ongoing pregnancy rate, live birth rate, embryo implantation rate, clinical pregnancy rate and biochemical pregnancy rate
Status: Phase III started
Milestone: NA
**Clinical Status, from previous page**

Merck began the single-blind, European Phase III ESPART trial to compare subcutaneous Pergoveris vs. Gonal-follitropin alfa in about 946 women who respond poorly to attempts at ovarian stimulation and are undergoing multifollicular development as part of an assisted reproductive technology treatment cycle. Pergoveris is approved in Europe to stimulate follicular development in adult women with severe LH and FSH deficiency. Merck markets Gonal-f, also an r-hFSH, for infertility.

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

Product: Secukinumab (AIN457)

Business: Autoimmune

Molecular target: Interleukin-17A (IL-17A)

Description: Human IgG1 mAb targeting IL-17A

Indication: Treat moderate to severe plaque psoriasis

Endpoint: Pharmacodynamics and safety

Status: Phase IIIb started

Milestone: NA

Novartis began the double-blind, international Phase IIIb CLEAR trial to compare 300 mg subcutaneous secukinumab once weekly for 4 weeks followed by once-monthly dosing in about 640 patients. Last October, Novartis submitted regulatory applications in the U.S. and EU for the product to treat moderate to severe plaque psoriasis (see BioCentury, Nov. 25, 2013). The pharma expects a decision from FDA and opinion from EMA’s CHMP on the applications next half. The product is also in Phase III testing to treat rheumatoid arthritis (RA), ankylosing spondylitis and psoriatic arthritis and in Phase II testing to treat multiple sclerosis (MS), asthma and uveitis. Data from Phase III trials of secukinumab in arthritic indications are expected in 2014. Johnson & Johnson (NYSE:JNJ, New Brunswick, N.J.) markets Stelara.

**Portola Pharmaceuticals Inc. (NASDAQ:PTLA), South San Francisco, Calif.**

Product: Andexanet alfa (PRT4445, PRT064445)

Business: Cardiovascular

Molecular target: NA

Description: Recombinant protein that reverses the anticoagulant activity of Factor Xa inhibitors

Indication: Reverse anticoagulant activity of Factor Xa inhibitors

Endpoint: Pharmacodynamics and safety

Status: Phase II started

Milestone: NA

Portola began a double-blind, placebo-controlled, dose-escalation Phase II trial to evaluate the ability of andexanet alfa to reverse the anticoagulant activity of edoxaban from Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568, Tokyo, Japan) in healthy volunteers. Subjects will receive 60 mg oral edoxaban once daily on days 1-6 and then be randomized to IV andexanet alfa or placebo on day 6. The first dose cohort will evaluate a 600 mg bolus dose of andexanet alfa. In June 2013, Portola partnered with Daiichi Sankyo to conduct the Phase II trial, which the pharma is funding.

Andexanet alfa is also in a Phase III trial to reverse the anticoagulant activity of Eliquis apixaban, a direct Factor Xa inhibitor, from Bristol-Myers Squibb Co. (NYSE:BMY, New York, N.Y.) and Pfizer Inc. (NYSE:PFE, New York, N.Y.). Portola has a number of deals to evaluate the ability of andexanet alfa to reverse the anticoagulation activity of marketed Factor Xa inhibitors (see BioCentury July 15, 2013; Jan. 20, 2014 & Feb. 10, 2014). Last year, FDA granted breakthrough therapy designation for andexanet alfa to reverse the anticoagulant activity of Factor Xa inhibitors. Portola said it is seeking accelerated approval for the product.

Edoxaban is approved as Lixiana in Japan to prevent venous thromboembolism (VTE) after major orthopedic surgery. In January, Daiichi submitted an MAA to EMA and an NDA to FDA for the direct Factor Xa inhibitor to prevent stroke and systemic embolic events in patients with non-valvular atrial fibrillation (AF); to treat deep vein thrombosis (DVT) or pulmonary embolism (PE); and to prevent recurrence of symptomatic VTE.

**Threshold Pharmaceuticals Inc. (NASDAQ:THLD), South San Francisco, Calif.**

Business: Cancer

Molecular target: Not available

Description: Hypoxia-activated cytotoxic 2-nitroimidazole prodrug of the DNA alkyator bromoisophosphoramide mustard (Br-IPM)

Indication: First-line treatment of advanced pancreatic cancer

Endpoints: Safety; progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), duration of overall response, levels of CA19-9, tumor metabolic activity assessed by PET scans and pharmacokinetics
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OFFERINGS & SECURITIES TRANSACTIONS

Week ended 3/28/14. Shares after offering refers to shares outstanding. Proceeds are gross, not net. Shares offered don’t include overallotments. Currency rates used in the week: C$=1.6494; €=1.3799; £=0.8895; SEK=0.1556

Completed Offerings

Advaxis Inc. (NASDAQ:ADXS), Princeton, N.J.
Business: Cancer, Infectious
Date completed: 3/26/14
Type: Follow-on
Raised: $14.1 million
Shares: 4.7 million
Price: $3
Shares after offering: 19 million
Underwriters: Aegis Capital; Noble Financial Capital Markets
Overallotment: 612,000
Note: The amount raised and share figures include the sale of a 612,000 share overallotment on March 28.

Antibe Therapeutics Inc. (TSX-V:ATE), Hamilton, Ontario
Business: Inflammation, Neurology, Autoimmune
Date completed: 3/28/14
Type: Private placement
Raised: C$3 million ($2.7 million)
Shares: 5 million
Price: C$0.60
Shares after offering: 34.9 million

Applied Genetic Technologies Corp. (NASDAQ:AGTC), Alachua, Fla.
Business: Gene/Cell therapy
Date completed: 3/26/14
Type: IPO
Raised: $50 million
Shares: 4.2 million
Price: $12
Shares after offering: 13.4 million
Underwriters: BMO Capital Markets; Wedbush; Cantor Fitzgerald; Roth Capital Partners
Overallotment: 625,000

Arch Biopartners Inc. (CNX:ACH), Toronto, Ontario
Business: Inflammation, Renal, Cancer
Date completed: 3/25/14
Type: Private placement of units
Raised: C$155,960 ($138,742)
Units: 557,000
Price: C$0.28 (unit)
Shares after offering: 49.6 million
Note: Each unit comprises a share and a two-year warrant to purchase a share at C$0.50.

CAP-CMV GmbH. Cologne, Germany
Business: Infectious
Date completed: 3/24/14
Type: Venture financing
Raised: €1.7 million ($2.3 million)
Underwriters: Credit Suisse; Citigroup; Cowen; RBC Capital Markets; Baird; Wedbush; Roth Capital Partners
Overallotment: 675,000

Endocyte Inc. (NASDAQ:ECTY), West Lafayette, Ind.
Business: Cancer, Diagnostic
Date completed: 3/27/14
Type: Follow-on
Raised: $94.5 million
Shares: 4.5 million
Price: $21
Shares after offering: 40.7 million
Underwriters: Credit Suisse; Citigroup; Cowen; RBC Capital Markets; Baird; Wedbush; Roth Capital Partners
Overallotment: 612,000

Generex Biotechnology Corp. (NASDAQ:GNE), Toronto, Ontario
Business: Drug delivery
Date completed: 3/27/14

See next page

Clinical Status,
from previous page

Status: Phase I started
Milestone: NA
Threshold said Merck began an open-label, dose-escalation, U.S. Phase I trial to evaluate 170-340 mg/m$^2$ IV TH-302 in combination with gemcitabine and Abraxane nab-paclitaxel on days 1, 8 and 15 of 28-day cycles in up to 48 patients with locally advanced unresectable or metastatic pancreatic adenocarcinoma. TH-302 is in the Phase III MAESTRO trial in combination with gemcitabine for the indication. The compound is also in Phase III testing in combination with doxorubicin to treat soft tissue sarcoma (STS). TH-302 has Orphan Drug designation in the U.S. and EU for STS and pancreatic cancer.


ZS Pharma Inc., Coppell, Texas
Product: ZS-9

Business: Hematology
Molecular target: NA
Description: Inorganic crystal form of zirconium silicate designed to trap potassium ions over other ions throughout the GI tract
Indication: Treat hyperkalemia
Endpoint: Maintenance of serum potassium levels for 28 days after establishment of normokalemia, defined as potassium levels of 3.5-5 mmol/L, for the first 48 hours and safety; proportion of patients who convert to normokalemia from hyperkalemia, defined as potassium levels of ≥5.1 mmol/L, after the first 48 hours
Status: Phase III started
Milestone: Submit MAA (1H15); submit NDA (1H15)

ZS Pharma began the international Phase III ZS004 trial to evaluate oral ZS-9 in about 275 patients with hyperkalemia. Patients will receive 10g ZS-9 thrice daily for 48 hours in the open-label acute phase. Patients who achieve normokalemia will then receive 5, 10 or 15 g ZS-9 once daily for 28 days in the double-blind, placebo-controlled maintenance phase. Patients are also eligible to enroll in the 60-day, open-label ZS004E extension study.

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BioCentury Week in Review

Completed Offerings, from previous page

Type: Private placement of units
Raised: $2.1 million
Units: 2,075
Price: $1,000 (unit)
Shares outstanding prior: 730.5 million
Investors: Institutional investors
Note: Each unit comprises a share of preferred stock and a five-year warrant to purchase up to 100% of the number of common shares issuable upon conversion of the preferred stock. The preferred stock initially converts at $0.03 and bears a 9% dividend until March 27, 2017, when the dividend rate will increase by 3% and each year thereafter.

Horizon Discovery Group plc (LSE:HZD), Cambridge, U.K.
Business: Functional genomics, Pharmacogenetics, Cancer
Date completed: 3/24/14
Type: IPO
Raised: £40 million ($66 million)
Shares: 22.2 million
Price: 180p
Shares after offering: 66.9 million
Note: Panmure Gordon acted as placement agent.

KinDex Pharmaceuticals Inc., Seattle, Wash.
Business: Endocrine/Metabolic, Inflammation
Date completed: 3/25/14
Type: Venture financing
Raised: $5 million
Investors: Polaris Partners; company management; individual investors

Kolltan Pharmaceuticals Inc., New Haven, Conn.
Business: Cancer, Antibodies
Date completed: 3/26/14
Type: Venture financing
Raised: $60 million
Investors: Institutional investor; KLP Enterprises; Deerfield Management; Franklin Berger; HBM Healthcare Investments; Purdue Pharma L.P.; Osage University Partners; C.T. Koll

Miraculins Inc. (TSX-V:MOM), Winnipeg, Manitoba
Business: Diagnostic, Proteomics
Date completed: 3/20/14
Type: Debt financing
Raised: $150,000 ($133,440)
Note: Miraculins issued a promissory note for $150,000 ($133,440) in the third tranche of a December 2013 secured loan for up to C$1 million ($899,600), bringing the total raised to C$550,000 ($514,698). The lender also received 74,758 shares of Miraculins common stock, plus an additional 17,172 shares of Miraculins common stock to correct a prior miscalculation. Miraculins raised C$250,000 ($230,501) in the first tranche and C$150,000 ($135,930) in the second tranche.

Business: Neurology
Date completed: 3/25/14
Type: Venture financing
Raised: $5.7 million
Investors: Existing investors; new investors
Note: NeuroPhage raised $5.7 million in the first tranche of a secured $17 million series D round.

Oasmia Pharmaceutical AB (SSE:OASM A), Uppsala, Sweden
Business: Cancer, Drug delivery, Veterinary
Date completed: 3/25/14
Type: Debt financing
Raised: SEK40 million ($6.2 million)
Note: The loan matures Aug. 31.

RuiYi Inc., La Jolla, Calif.
Business: Autoimmune, Cancer
Date completed: 3/27/14
Type: Venture financing
Raised: $15 million
Investors: 5AM Ventures; Versant Ventures; Apposite Capital; SR One; MS Ventures; Aravis Venture

Scilex Pharmaceuticals Inc., West Chester, Pa.
Business: Neurology
Date completed: 3/21/14
Type: Venture financing
Raised: $5 million
Placement agent: Aegis Capital

scPharmaceuticals LLC, Boston, Mass.
Business: Drug delivery, Cardiovascular
Date completed: 3/26/14
Type: Venture financing
Raised: $16 million
Investors: 5AM Ventures; Lundbeckfond Ventures; individual investors
Note: The financing is a tranched series A round.

Transgene S.A. (Euronext:TNG), Illkirch, France
Business: Cancer, Infectious
Date completed: 3/25/14
Type: Rights offering
Raised: €45.5 million ($62.8 million)
Shares: 4.6 million
Price: €10
Shares after offering: 38.4 million
Investors: Institut Merieux; existing investors
Note: Shareholders were eligible to purchase one share for every seven held.

Date completed: 3/25/14
Type: Private placement
Raised: €20 million ($27.6 million)
Shares: 2 million
Price: €10
Shares after offering: 38.4 million
Investors: Institutional investors

Verona Pharma plc (LSE:VRP), London, U.K.
Business: Inflammation, Pulmonary
Date completed: 3/24/14
Type: Placing and open offer
Raised: £14 million ($23.1 million)
Shares: 637.3 million
Price: 2.2p
Shares after offering: 1 billion
Note: The offering comprised £6.6 million ($10.8 million) in a placing; £6.4 million ($10.6 million) in a subscription to Wales Life Sciences Investment Fund and another investor; and £1 million ($1.7 million) in an open offer, in which shareholders were eligible to purchase one share for every eight held.

Vigilant Biosciences Inc., Miami, Fla.
Business: Diagnostic
Date completed: 3/25/14
Type: Venture financing
Raised: $300,000
Investor: Florida Institute for Commercialization of Public Research
Note: The offering is a loan.

Date completed: 3/25/14
Type: Venture financing
Raised: $2 million
Investors: New investors; company founder

Proposed Offerings

Ariosa Diagnostics Inc., San Jose, Calif.
Business: Diagnostic
Date announced: 3/24/14
Type: IPO
To be raised: Up to $69 million
Shares: TBD
Price: TBD
Underwriters: JPMorgan; Citigroup; Leerink Partners; William Blair
Note: Ariosa is seeking to list its shares on NASDAQ.

Cellectis S.A. (Euronext:ALCLS), Paris, France
Business: Gene/Cell therapy, Genomics
Date announced: 3/25/14
Type: Placing
To be raised: €20.5 million ($28.3 million)
Shares: 4 million
Price: €5.13
Shares outstanding prior: 20.8 million
Investors: Orbimed Advisors; venBio; Ridgeback Capital; Aquilo Capital; Merlin Nexus; and other investors

Karyopharm Therapeutics Inc. (NASDAQ:KPTI), Natick, Mass.
Business: Cancer, Inflammation
Date announced: 3/24/14
Type: Follow-on
To be raised: Up to $115 million
Shares: TBD
Price prior: $42.07
Underwriters: BoFA Merrill Lynch; Leerink Partners; Wedbush; JMP Securities; Oppenheimer

Lorus Therapeutics Inc. (TSX:LR; Pink:LRUSF), Toronto, Ontario
Business: Cancer, Gene/Cell Therapy
See next page
**Mapi-Pharma Ltd.**, Ness Ziona, Israel
Business: Drug delivery, Generics  
Date announced: 3/26/14  
Type: IPO  
To be raised: Up to $46 million  
Shares: TBD  
Price: TBD  
Underwriter: Aegis Capital  
Note: Mapi-Pharma plans to list its shares on NASDAQ.

**PledPharma AB** (SSE:PLED), Stockholm, Sweden  
Business: Cancer, Cardiovascular  
Date announced: 3/24/14  
Type: Rights offering  
To be raised: Up to SEK20.2 million ($3.2 million)  
Shares: 1.7 million  
Price: SEK12  
Placement agent: Sedermera Fondkommission  
Shares outstanding prior: 21.9 million  
Investors: Existing investors; company management; company directors  
Note: Shareholders are eligible to purchase one share for every 13 held.

**Syndax Pharmaceuticals Inc.**, Waltham, Mass.  
Business: Cancer  
Date announced: 3/27/14  
Type: IPO  
To be raised: Up to $69 million  
Shares: TBD  
Price: TBD  
Underwriters: Deutsche Bank; Jefferies; JMP Securities; Wedbush  
Note: Syndax is seeking to list its shares on NASDAQ.

**Adamas Pharmaceuticals Inc.**, Emeryville, Calif.  
Business: Neurology, Infectious  
Date announced: 3/26/14  
Type: IPO  
To be raised: Up to $54 million  
Shares: 3 million  
Price: $16-$18  
Underwriters: Credit Suisse; Piper Jaffray; William Blair; Needham  
Overallotment: 450,000  
Note: Adamas amended its IPO on NASDAQ and now plans to sell 3 million shares at $16-$18. Earlier this month, the company filed to raise up to $69 million in the offering.

**Corium International Inc.**, Menlo Park, Calif.  
Business: Drug delivery  
Date announced: 3/24/14  
Type: IPO  
To be raised: Up to $66 million  
Shares: 5.5 million  
Price: $10-$12  
Underwriters: Jefferies; Leerink Partners; Needham; FBR  
Overallotment: 825,000  
Note: The company amended its IPO on NASDAQ and now plans to sell 5.5 million shares at $10-$12. Earlier this month, Corium filed to raise up to $50 million in the offering.

**Actinium Pharmaceuticals Inc.** (NYSE-M:ATNM), New York, N.Y.  
Business: Cancer  
Date announced: 3/26/14  
Actinium transferred its listing to NYSE MKT under the symbol “ATNM.” Previously, the stock traded on the OTCQB.

**Akebia Therapeutics Inc.** (NASDAQ:AKBA), Cambridge, Mass.  
Business: Hematology, Cardiovascular  
Date announced: 3/26/14  
Akebia raised $15 million through the sale of 879,647 shares at $17 to cover the overallotment from its March 20 IPO, bringing the total raised to $115 million. The company, which closed Friday at $20, has 20.1 million shares outstanding.

**Dyax Corp.** (NASDAQ:DYAX), Burlington, Mass.  
Business: Inflammation, Ophthalmic  
Date announced: 3/26/14  
Dyax raised $11.1 million through the sale of 1.2 million shares at $9.25 to cover the overallotment from its March 14 follow-on, bringing the total raised to $85.1 million. The company, which closed Friday at $8.48, has 135.7 million shares outstanding.

**Versartis Inc.** (NASDAQ:VSAR), Redwood City, Calif.  
Business: Endocrine/Metabolic  
Date announced: 3/26/14  
Versartis raised $18.9 million through the sale of 900,000 shares at $21 to cover the overallotment from its March 20 IPO, bringing the total raised to $144.9 million. The company, which closed Friday at $29.94, has 24.3 million shares outstanding.

**Ipsen Group** (Euronext:IPN; Pink:IPSEY), Boulogne-Billancourt, France  
Business: Cancer, Endocrine/Metabolic, Neurology  
Date announced: 3/20/14  
Ipsen said shareholder Mayroy raised €173.7 million ($241.1 million) through the sale of 5.9 million Ipsen shares, or about a 7% stake, at €29.50 in a private placement. Ipsen purchased 842,542 of its shares from Mayroy for cancellation. Mayroy now has a 57.6% stake in Ipsen. Ipsen, which closed Friday at $29.75, has 83.4 million shares outstanding.

**MediWound Ltd.** (NASDAQ: MDWD), Yavne, Israel  
Business: Dermatology  
Date announced: 3/26/14  
MediWound raised $10.5 million through the sale of 750,000 shares at $14 to cover the overallotment from its March 20 IPO, bringing the total raised to $80.5 million. The company, which closed Friday at $15.10, has 21.1 million shares outstanding.

**Ipsen** Group (Euronext:IPN; Pink:IPSEY), Boulogne-Billancourt, France  
Business: Cancer, Endocrine/Metabolic, Neurology  
Date announced: 3/20/14  
Ipsen said shareholder Mayroy raised €173.7 million ($241.1 million) through the sale of 5.9 million Ipsen shares, or about a 7% stake, at €29.50 in a private placement. Ipsen purchased 842,542 of its shares from Mayroy for cancellation. Mayroy now has a 57.6% stake in Ipsen. Ipsen, which closed Friday at $29.75, has 83.4 million shares outstanding.