THE 21CC SOLUTION

BY STEVE USDIN, WASHINGTON EDITOR

The U.S. House of Representatives is in the middle of its effort to create legislation intended to promote biomedical innovation, and the Senate is just starting a similar effort, but it is already possible to anticipate the provisions that could be in any law that results from the efforts, and with greater confidence, the proposals that will not be included.

As the House Energy and Commerce Committee (E&C) works to pare down its sweeping 21st Century Cures legislation, the Senate Health, Education, Labor and Pensions Committee (HELP) is embarking on a less ambitious “innovation initiative” that is intended to produce companion legislation.

In the end, it all will come down to a simple equation: Start with a large number of policy options, subtract any that don’t appeal to Republicans, remove any that Democrats adamantly oppose, delete any that industry hates, and kill or revamp those that FDA says it cannot live with. Then examine the product and punt any FDA-related provisions that require money or manpower to implement into upcoming user fee negotiations, and scale back any others that are expensive.

There are several ways to solve the equation. The solution set could include the creation of a pathway for approving antibiotics for limited populations based on small, pathogen-specific studies.

If the criteria are tightly defined, it is also possible to persuade Congress to provide extended market exclusivity for drugs for serious unmet needs such as Alzheimer’s disease (AD), and to add exclusivity to drugs approved for common conditions if sponsors conduct research that leads to the addition of an Orphan indication.

It also would be possible to reach consensus on some policies to improve the development of medicines for children, including the creation of global pediatric clinical trials.
It is far from certain, however, that Congress will produce a solution that satisfies all of the criteria for success, or that it will do so in time to avoid the legislative paralysis that will afflict Washington early next year as the presidential race heats up.

Even if the efforts to create a new law ultimately fail, the debate and thinking that are going into the 21st Century Cures and innovation initiatives will live on in the drug and device user fee reauthorization legislation that will be enacted in 2017.

Moreover, many of the topics that have been included in a discussion draft of 21st Century Cures legislation could be effectively addressed without legislation, either by FDA or NIH acting alone, or through collaboration between government and representatives from medical product manufacturers, patients and patient advocates, and academic scientists. Areas that are ripe for action outside the legislative arena include patient-driven drug development and biomarker and surrogate endpoint validation.

**INNOVATION INITIATIVE**

The House and Senate processes are a study in contrasts.

The House E&C Committee has sought maximum publicity, launching a social media campaign and making bold claims about Congress’ ability to transform medical product discovery and development. E&C has held 19 round table discussions and eight hearings. Stakeholders have invested a massive amount of time in the 21st Century Cures process.

The initial result of all of this work is a 393-page discussion draft that is a mash-up of hundreds of proposals from a number of bills that have been introduced over the last year, most poorly or incompletely drafted, many contradictory, and none vetted with the agencies responsible for implementation.

The Senate HELP Committee is taking a more traditional, low key approach and pursuing more modest goals.

Speaking at the first hearing on the innovation initiative last Tuesday, Sen. Lamar Alexander (R-Tenn.) made it clear that the effort is a lower priority for him than 21st Century Cures is for E&C Chairman Fred Upton (R-Mich.).

Alexander, who is the HELP chairman, did not convey a sense of urgency, saying he plans to have a bill passed by the Senate in “about a year,” a timetable that would not allow Upton to meet his objective of having legislation on President Obama’s desk by year end. That means the entire effort would land in the legislative dead zone that will form in the wake of the presidential campaign.

Alexander started the hearing by saying the committee’s first priority is “fixing” the No Child Left Behind Act; its second is reauthorizing the Higher Education Act; “and third, one we’re all looking forward to without exception, improving biomedical innovation, including the Food and Drug Administration and the National Institutes of Health.”

None of the HELP members at the hearing presented a clear vision for the innovation initiative, and their questions and comments indicated a tenuous grasp of the regulatory and scientific issues at the core of FDA’s and NIH’s missions.

Sen. Orrin Hatch (R-Utah), the HELP Committee member with the deepest knowledge of FDA and the best track record of pushing ambitious medical products legislation through Congress, was conspicuous by his absence.

**DIY PATIENT ENGAGEMENT**

The House Energy & Commerce Committee captured the biomedical public policy zeitgeist by putting patient-focused drug development at the top of the 21st Century Cures discussion draft.

It missed the essence of the concept, however, by attempting to legislate in an area where by definition patients and their advocates should be taking the lead.

Almost everyone involved with medical product development and regulation already agrees that steps should be taken to better integrate patient perspectives throughout development and regulation. The open question is what steps can advance the goal.

One place to start is for patient advocacy groups and drug developers to collaborate on a set of proposed draft guidance documents and submit them to FDA.

The guidances would set standards for the scientific collection and analysis of patient preference data, specify how such data could be submitted to FDA, and indicate how the agency should integrate it into assessments of benefit-risk.

The draft guidances could also identify best practices for companies to interact with individual patients and patient advocacy groups in ways that do not run afoul of prohibitions against promotion of experimental drugs or off-label uses.

The Medical Device Innovation Consortium, a partnership that includes FDA, medical device companies, patient groups and academic researchers, is laying some of the groundwork. It is assembling a catalog of methods for assessing patient preferences about benefits and risks and creating a framework to incorporate preferences into benefit-risk assessments.

Patient advocacy groups and drug companies could start working on draft guidances immediately, with no intervention by Congress. By starting the drafting process, patients and drug developers would have more control over the outcome than they would if they were responding to a document drafted by FDA.

— STEVE USDIN
Alexander implicitly criticized E&C’s unruly discussion draft, saying, “We don’t want to waste our time in the next year; we can’t do everything.” The lawmaker asked outgoing FDA Commissioner Margaret Hamburg and NIH Director Francis Collins to identify “one or two or three things we should focus on in order to make the greatest contribution to the goal of moving medicines, devices and treatments to the medicine cabinet and doctor’s office.”

**POLITICAL REALITIES**

Upton stresses bipartisanship every time he discusses the 21st Century Cures initiative, but so far has failed to gain the public support of a single Democrat. The discussion draft is being reworked to make it palatable to the other side of the aisle.

Alexander also said his innovation initiative will be bipartisan. But beating any legislation into a form congressional Democrats and the Obama administration will accept will not be easy. To obtain support from Democrats and the White House, numerous provisions in the House discussion draft that set FDA’s hair on fire will have to be dropped or revamped.

FDA has briefed E&C staff on scores of specific items the agency opposes, including some it views as existential threats to its ability to protect the public from unsafe medical products, and others that the agency believes would paralyze medical product reviews.

These include provisions that would require FDA to make decisions based on peer-reviewed journal articles and bar it from requesting the underlying data, and others that lower standards for the kinds of data that support regulatory decisions.

The House committee’s efforts to accelerate the validation of biomarkers could suck up vast amounts of time from product reviewers and require the agency to make decisions on timetables that its senior leaders believe are completely unrealistic.

Given the close relationships between Republican lawmakers’ staffers and pharma companies, anything industry strongly opposes, such a proposal in the discussion draft to fund NIH and patient assistance programs through levies on drug sales, is certain to be vaporized.

Provisions that would harm influential Democratic constituencies, such as the generic drug industry, also are unlikely to make it to President Obama’s desk. This means any new market exclusivities will have to be narrowly focused and framed in ways that do not make them seem to be giveaways to big pharma.

At last week’s HELP hearing, every Democrat who attended, as well as several Republicans, said that increasing NIH’s budget is a high priority. House Democrats on the E&C Committee have made increased NIH funding a prerequisite for their support of 21st Century Cures legislation.

However, unless some creative new revenue source other than taxpayer dollars is identified, increased appropriations for NIH would have to be negotiated with appropriations committees in both the House and Senate. Appropriators are likely to want any increases to be paid for with equivalent cuts to programs under the jurisdiction of E&C and HELP. This robbing Peter to pay Paul approach would limit the size of any increase and put the legislation at risk from constituencies that would be hurt by the cuts.

There also will be strong pressure to defer action on any proposals that require new funding for FDA, leaving them for negotiations over drug and device user fees, which have become a relatively transparent and collegial process.

The need to avoid contentious issues means Congress is unlikely to tackle one of pharma’s most pressing concerns, making FDA’s regulation of commercial speech, including the use of social media, consistent with the First Amendment to the U.S. Constitution.

Congress is also unlikely to tackle the ticklish issue of oversight of laboratory developed tests, though it might find a way to delay FDA from moving ahead with its plans to regulate LDTs.

“**WE DON’T WANT TO WASTE OUR TIME IN THE NEXT YEAR; WE CAN’T DO EVERYTHING.**”

**SEN. LAMAR ALEXANDER (R-TENN.)**

**SOLVING THE EQUATION**

When everything that doesn’t fit into the political equation is stripped out, a few items remain. They wouldn’t be revolutionary, but they would allow politicians to honestly claim that they are helping Americans get access to new and better medicines.

Creating a public-private partnership that would advance patient-driven drug development is non-controversial. Its agenda could include conducting research on methods for determining patient preferences that can be used to choose endpoints and evaluate benefit-risk trade-offs; setting standards for patient-reported outcomes and other patient-centered research, and elucidating best practices for patient engagement. Funding and a mandate from Congress would make it easier to achieve the scale needed to make progress quickly, but this work could start without legislation.

Measures to reduce the red tape wrapped around clinical trials by reforming informed consent and IRB procedures are good candidates for making it through the political process. This could increase participation in trials and facilitate research using electronic health records and databases of genomic information.

Congress and the White House understand the threat posed by antibiotic-resistant bacteria, so FDA’s proposal to create a new pathway to speed antibiotics to market for limited populations will be included in 21st Century Cures legislation, or if doesn’t make it over the finish line, in PDUFA reauthorization.

The broad, generous extensions of market exclusivity proposed in the House discussion draft will not pass muster with Democrats, but it could be possible to achieve consensus on exclusivity provisions that are tightly defined, for more modest time periods and clearly designed to serve very specific goals. These include incentives for adding Orphan indications...
to drugs approved for common diseases, and developing compounds for public health priorities such as Alzheimer’s.

New market monopolies would be more politically acceptable if they are created as pilot projects, with short expiration dates. Experience with the Orphan Drug Act and PDUFA demonstrates the value of reconsidering and reauthorizing policies on a periodic basis.

There is broad support for creating a pathway for approving antibiotics based on small data sets for limited populations.

NIH Director Collins has asked Congress to reduce administrative burdens on NIH-funded extramural researchers, and to ease oversight of and restrictions on travel by NIH intramural scientists. These are small common sense requests that are not likely to be opposed. They would boost morale on the NIH campus and free resources that now are being wasted on paper-pushing.

Advocates for pediatric drug development have good arguments supporting the need for legislation and have sympathetic ears in Congress.

PhRMA’s letter added, “EBA approval would entail sponsor and FDA post-market confirmation of safety and effectiveness and enhanced safety monitoring by FDA.”

MOVING AHEAD WITHOUT CONGRESS

Given the limited chances that 21st Century/innovation initiative legislation will actually make it into law, and the lengthy lead time for enactment of new policies tied to user fees, it makes sense to look for opportunities to advance key priorities without waiting for Congress.

Hamburg, in her last testimony before Congress as FDA commissioner, mentioned some areas where steps could be taken to improve the way drugs are developed and regulated. Major advances could be made in each of them without legislation through actions FDA can take on its own or through cooperation with academic scientists, patient groups and industry.

“TREATMENTS CAN BETTER MEET THEIR NEEDS IF WE CAN CAPTURE SCIENCE-BASED, DISEASE-SPECIFIC PATIENT INPUT TO INCORPORATE IN THE DEVELOPMENT AND REVIEW PROCESS.”

MARGARET HAMBURG, FDA

Possibilities for helping children in 21st Century Cures/innovation legislation include supporting the establishment of global pediatric clinical trial networks, which would widen access to small patient populations and facilitate harmonized data requirements.

Congress could also act on proposals to reform the Pediatric Research Equity Act — which requires companies to study drugs for some conditions in children — to make the law more applicable to pediatric cancer. Key issues are modifying a waiver for Orphan conditions and classifying cancer therapies by targeted genomic mutation rather than tumor location.

The breakthrough therapies program has been wildly popular, so efforts to extend the concept could be successful.

In a letter to the HELP Committee, PhRMA proposed the creation of an Expedited Breakthrough Approval (EBA) authority. The authority would “enhance the existing Breakthrough designation for qualified new medicines by authorizing FDA and sponsors to convert strong, early stage clinical trial results to full approvals for cases of serious, life-threatening diseases where there is no adequate available treatment for patients.”

REFERENCES


ZARXIO TEA LEAVES

BY ERIN MCCALLISTER, SENIOR EDITOR

As the first approved U.S. biosimilar, Zarxio filgrastim-sndz from Novartis AG’s Sandoz unit will give a glimpse at the discount size for biosimilars and how the innovator company responds to the competition. But questions about how naming and interchangeability will affect biosimilar uptake won’t be answered until 2017, when a pharmacy-dispensed, chronic use biosimilar is due to hit the market.

On March 6, FDA approved Zarxio for all five the indications for which Amgen Inc.’s Neupogen filgrastim is approved: to decrease the risk of infection in patients undergoing chemotherapy; reduce the time to neutrophil recovery following chemotherapy; reduce the duration of neutropenia in patients undergoing bone marrow transplant; mobilize autologous hematopoietic progenitor cells for leukapheresis; and reduce the incidence and duration of severe neutropenia.

Sandoz expects to launch Zarxio within the next month, almost five years after the biosimilars pathway was created by the Affordable Care Act. Zarxio won’t be interchangeable with Neupogen, which means that pharmacists can’t substitute for the innovator drug without the physician’s consent. But this isn’t expected to have much effect on uptake because it is a physician-administered drug.

For the same reason, the suffix at the end of Zarxio’s non-proprietary name is also likely to be less of an issue. Biosimilars manufacturers had been concerned that a different name could be a barrier to substitution at the pharmacy level. And while it could still affect physician perceptions of Zarxio’s safety, it is unclear how permanent the name is. At the time of approval, FDA said the filgrastim-sndz name is a “placeholder” while the agency drafts guidance on the topic, which is due out this year.

The best test case for interchangeability and naming will likely come with the approval of the first biosimilar version of AbbVie Inc.’s Humira adalimumab, which appears to be the first chronic-use, pharmacy-dispensed biosimilar in the queue.

At least two companies are developing biosimilars of the human mAb against TNF alpha. Amgen has completed pivotal studies of its ABP 501, and could launch the biosimilar in 2017. Sandoz also has a biosimilar of Humira in development.

In the meantime, payers will be watching Zarxio’s launch to see how steep Sandoz will go when it comes to discounts and whether Amgen matches the discount or uses direct-to-consumer marketing or bundling to hold onto its market share.

PEGGING PRICE

Zarxio’s price won’t be known until closer to launch, but physicians and payers who spoke to BioCentury hope it is low enough to force prices down and improve access.

“WE’LL BE LOOKING AT THIS AS A TEST CASE TO GAUGE WHAT THE REACTION IS FROM A PRESCRIBER STANDPOINT AND WHAT THEIR WILLINGNESS TO USE IT WILL BE.”

STEVEN JOHNSON, PRIME THERAPEUTICS

The launch date depends on litigation between Sandoz and Amgen, which has alleged that Sandoz refused to comply with the Biologics Price Competition and Innovation Act of 2009 when it filed its BLA for Zarxio.

Last week, the U.S. District Court for the Northern District of California accepted motions from the companies. Amgen submitted a motion for a preliminary injunction that would prevent Sandoz from marketing Zarxio. Sandoz is seeking to dismiss Amgen’s claims. The judge did not set the next hearing date.

Novartis said the companies have agreed to jointly request an expedited review if the case is appealed to the U.S. Court of Appeals of the Federal Circuit (CAFC).

Sandoz has agreed not to launch Zarxio in the U.S. until the earlier of April 10 or a ruling in its favor.

Sandoz declined to discuss price, but at a January FDA panel meeting on Zarxio, Mark McCamish, global head of biopharmaceuticals and oncology injectables development, said the list price may be the same as Neupogen, but “the cost will be less to the consumer, to the payer, to the healthcare economy. It has to be. Otherwise, it doesn’t make sense.”

Payers have anticipated that the net discount on Zarxio, and biosimilars in general, will be about 20-30%, similar to what it is in Europe.

The wholesale acquisition cost (WAC) of Neupogen is $314.80 for a 0.5 mL vial, or about $4,407 for a 14-day course for a 60 kg patient undergoing chemotherapy.

Obviously, the larger the discount, the more likely payers and subsequently physicians will be to adopt the biosimilar. However, Neupogen is no longer considered standard of care (SOC) for the largest indication for which it is approved — to reduce the risk of infection in patients undergoing chemotherapy — which could mean Sandoz has to offer discounts of 30% or more.
According to John Glaspy, a physician in the department of hematology oncology at UCLA Jonsson Comprehensive Cancer Center, Amgen's Neulasta pegfilgrastim is SOC because it only requires a single dose per chemotherapy cycle.

The WAC for Neulasta is $4,466.35 per dose. As a physician-administered drug like Neupogen, Neulasta is purchased by the oncologist or hospital and reimbursed by payers at ASP plus 6%. While Neulasta's WAC may be higher than a full course of Neupogen, Glaspy said payers have pushed doctors to use Neulasta because the drug requires fewer office visits and thus reduces total costs.

If the Sandoz discount equates to about $1,500 per month less, or about 35% off Neupogen's WAC, resulting in lower co-pays, Glaspy said it might be enough to convince the patient to come in every day for an injection—or for payers to force patients to do so.

“It’s not inconceivable that a tipping point would be reached where it is more cost-effective to do daily injections,” he said.

Neupogen is still used for other indications for which Neulasta is not approved, including the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Although Sandoz is developing a biosimilar version of Neulasta, spokesperson Julie Masow told BioCentury the company decided to seek approval of Zarxio first because it has been marketing the drug outside the U.S. since 2009. She said the biosimilar has over 30% market share in Europe, where it is known as Zarzio, and has surpassed Neupogen for market share in the region.

Drugs reimbursed at ASP plus 6% typically mean that doctors are less inclined to prescribe a cheaper alternative; however, Glaspy said he is hopeful that competition will drive the price down and allow doctors to treat more patients.

He estimated that 30% of patients who are on chemotherapy and should be receiving Neupogen or Neulasta either aren't getting the drug or are getting suboptimal chemotherapy doses.

“One way to reduce the risk of infection is to inadequately dose the chemo. If an oncologist was worried about infection but the patient couldn't afford or didn't want to use filgrastim, the doctor would just decrease the dose of chemo. But if these drugs cost less, payers wouldn't be fighting it and more people could get treated,” Glaspy said.

“I would hope that we would see not only increased access because of lower cost, but also less cost would be passed onto the patients,” said Gary Lyman, oncologist, health economist and co-director of the Fred Hutchison Cancer Center.

In Europe, Masow said, “Introduction of biosimilars has played an important role in increasing access to filgrastim without increasing total spend.”

The oncologists also don’t think the unique non-proprietary name for Zarxio will deter physicians.

“There might be a slightly slower lag time than with generics, but I don’t think it will have a big effect,” Lyman said.

**PAYERS WEIGH IN**

While payers are eager to see the price of Zarxio, they don’t expect the first biosimilar to make a huge dent in healthcare costs.

Steven Johnson, senior director of health outcomes at pharmacy benefit manager Prime Therapeutics LLC, said Neupogen only makes up 10-20% of the PBM’s book of business for the neutropenia and supportive care indications, with the lion’s share going to Neulasta.

“If the price is low enough, it might be a reason to drive physicians towards Zarxio and potentially even away from Neulasta,” he said. “However, we’ll be looking at this as a test case to gauge what the reaction is from a prescriber standpoint and what their willingness to use it will be.”

Amgen reported 2014 U.S. sales of $839 million for Neupogen and $3.6 billion for Neulasta.

Michael Sherman, CMO at regional payer Harvard Pilgrim Health Care LLC, was more optimistic.

The expected 20-30% discount for Zarxio “is meaningful for an expensive drug like Neupogen,” Sherman said.

Prime wouldn’t say how it would change its formulary based on Zarxio’s price.

**“AMGEN COULD REDUCE THEIR PRICE AND MAKE IT HARD FOR PAYERS TO PREFER THE BIOSIMILAR.”**

**MICHAEL SHERMAN, HARVARD PILGRIM**

Harvard Pilgrim, which has both open and closed formularies, said it would consider excluding Neupogen from its closed formulary.

“If the biosimilar does have a price advantage, it is likely that we will take steps on the formulary. With the open formulary, we could theoretically put them both on there but have the new Sandoz drug at a lower tier with a lower cost share. We could also require step therapy,” Sherman said. “For our closed formulary, we could only list the Sandoz drug.”

Sumit Dutta, SVP and CMO at Catamaran Corp., said the PBM also will consider step therapy and other preferred drug strategies “to promote the most cost-effective therapy.”

However, Harvard Pilgrim is less likely to change its coverage of Neulasta in response to Zarxio.

“If it would have to come in a lot lower on price than we are expecting to make a difference. Even then, it is unlikely that we would exclude it. We could do some sort of tiering or cost-sharing incentive, but I think we’d be unlikely to say that doctors can only use one agent when it has a more cumbersome route of dosing,” Sherman told BioCentury.

Dutta didn’t say how the launch of Zarxio would affect Catamaran’s coverage of Neulasta.

With savings from Zarxio expected to be modest, payers think the first biosimilar to deliver tangible cost savings will be CT-P13 from Hospira Inc. and Celltrion Inc. CT-P13 is under FDA review as a biosimilar of...
Johnson & Johnson’s Remicade infliximab, a physician-administered, chronic-use autoimmune drug.

“Remicade is frequently among the top one, two or three drugs in spend on the medical side,” Prime’s Johnson said.

AMGEN’S RESPONSE
The biggest takeaway from Zarxio’s launch could lie in Amgen’s response to the lower priced-alternative.

“Price will be a driving factor. If there isn’t a big differential or if that differential is closed by the innovator company, the launch of the biosimilar could be not as consequential as people think,” said Dan Mendelson, CEO and founder of healthcare consultancy Avalere Health LLC.

Sherman agreed. “Amgen could reduce their price and make it hard for payers to prefer the biosimilar,” he said.

Alternatively, if Amgen has portfolio rebates in place with payers for its cancer supportive care drugs, it could be difficult for Sandoz to offer a big enough discount to entice payers to switch, as it is possible the rebates across the portfolio are large enough to offset any potential gains a payer may get from using Zarxio instead of Neupogen.

Mendelson was optimistic prices would still come down. “Whenever markets become more competitive, prices come down. It’s inevitable,” he said.

Amgen declined to say if it has portfolio deals with payers for its supportive care products.

As for how Amgen is thinking about Zarxio’s launch, spokesperson Kristin Davis noted the biosimilar has shown efficacy in only one of the five indications — chemotherapy-induced neutropenia — and that “biosimilars should be treated like any other biologic therapy with the decision to use a biologic based on clinical evidence of efficacy and safety and the true cost as demonstrated by each individual product.”

Sherman said he also will be watching what Amgen does with direct-to-consumer marketing to help retain patients.

“I could picture something that glosses over the issue and suggests that the two drugs aren’t the same thing and urges patients to ‘ask your doctor.’ It is hard to say how that will play and how susceptible patients will be to this messaging. Patients don’t want to hear that they’re getting a drug that is almost as good,” he said.

At least two other biosimilars for Neupogen and Neulasta could be available in the next year. Apotex Inc. has submitted biosimilar applications to FDA for both drugs.

COMPANIES AND INSTITUTIONS MENTIONED
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Apothex Inc., Toronto, Ontario
Avalere Health LLC, Washington, D.C.
Catamaran Corp. (NASDAQ:CTR; TSX:CCT), Schaumburg, Ill.
Celltrion Inc. (KOSDAQ:068270), Incheon, South Korea
Fred Hutchinson Cancer Research Center, Seattle, Wash.
Harvard Pilgrim Health Care LLC, Boston, Mass.
Hospira Inc. (NYSE:HSP), Lake Forest, Ill.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Prime Therapeutics LLC, Eagan, Minn.
UCLA Jonsson Comprehensive Cancer Center, Los Angeles, Calif.

REFERENCES
AbbVie Inc.’s failed attempt to buy Shire plc last year was based on the expected savings from tax inversion and the opportunity to diversify its pipeline. This time around, the pharma’s purchase of Pharmacyclics Inc. is treading more familiar territory: augmenting its hematologic oncology pipeline with a marketed drug with enormous potential and a sales team to support it.

If successful, AbbVie will create the same kind of franchise with Imbruvica ibrutinib that it created in autoimmune disease with Humira adalimumab. On a March 12 investor call, Chairman and CEO Richard Gonzalez said AbbVie would get its money’s worth from the $21 billion deal to acquire Pharmacyclics by building Imbruvica, which he described as a “pipeline in a drug,” into a franchise, just as it did with Humira.

“It’s a mechanism that looks to be broadly applicable across B cell malignancies, and potentially even further than that. Much like how Humira was expanded across the anti-TNF indications,” he said.

Pharmacyclics has guided for $1 billion in sales this year, and clinical trials of Imbruvica will report data this year that could support its use in earlier therapy lines and new hematologic cancer indications.

AbbVie said it expects the transaction to be accretive beginning in 2017 and to exceed the cost of capital hurdle rate by 2019.

Acquiring Pharmacyclics will add a second revenue source to Humira, which accounts for over half of AbbVie’s sales.

The human mAb against tumor necrosis factor (TNF) alpha will face patent expirations beginning in 2016, although an average of three analyst projections suggest Humira sales will fall only modestly, from a peak of about $16 billion in 2017 to $15 billion in 2020.

Gonzalez said Imbruvica’s patent protection will last until 2027 in the U.S. and to 2029 in the EU.

Imbruvica is a Bruton’s tyrosine kinase (Btk) inhibitor that covalently binds to cysteine residue 481. Btk is a component of the B cell receptor signaling pathway that induces tumor expansion and proliferation; it is also a mediator of inflammatory pathways in B cells and myeloid cells.

Though Imbruvica is first in class, it’s not expected to be as big a product as Humira. The drug is approved in the U.S. to treat all lines of Waldenstrom’s macroglobulinemia (WM) and chronic lymphocytic leukemia (CLL) in patients with 17p deletion. It is approved second-line to treat CLL and mantle cell lymphoma (MCL). Imbruvica has accelerated approval for MCL.

Last year, Pharmacyclics reported net product revenue of $492 million from Imbruvica. Consensus estimates project global sales of $8.3 billion in 2025.

Moreover, AbbVie will have to split profits with Johnson & Johnson. Under a 2011 deal, Pharmacyclics and J&J’s Janssen Biotech Inc. unit share development costs 40/60 and pretax commercial profits and losses equally. Janssen has co-exclusive rights in the U.S. and exclusive ex-U.S. rights to Imbruvica. The deal excludes inflammation and immune-mediated conditions.

On the March 5 call to discuss the acquisition, Gonzalez said AbbVie expects its share of Imbruvica’s annual sales to peak at over $7 billion. On the March 12 call, Gonzalez laid out AbbVie’s expectations for how Imbruvica would reach its numbers: a quarter would stem from continued use in established indications and 40% from moving up in lines of therapy — he predicted Imbruvica would achieve a 65% peak market share. In addition, 20% of the growth would come from new blood cancer indications, and the rest from expanding into non-hematological indications, such as solid tumors or graft-versus-host disease (GvHD).

Jonathan Gertler, CEO of strategic and financial consulting firm Back Bay Life Science Advisors, told BioCentury he thought AbbVie’s bid would prove “cogent” in the long run, given the shift in the oncology market from cytotoxic agents to over 50% targeted agents.

“On one hand they’re buying only half a drug, but on the other hand they’re buying a cancer pipeline,” he said.

Furthermore, Gertler thought owning a blockbuster blood cancer drug would give AbbVie leverage to aggregate additional programs.

“I think when you put a gauntlet down like this and enter that space, if other assets come along it puts you in a phenomenal position to be the most competitive bidder for those as well,” he said.

On the March 12 call, Gonzalez said AbbVie doesn’t expect to make another $20 billion acquisition in the near term, but is open to smaller asset-based acquisitions in its areas of focus.
Behind Imbruvica, Pharmacyclics has three compounds: abexinostat, a histone deacetylase (HDAC) inhibitor in Phase II testing to treat hematologic cancers; PCI-27483, a subcutaneous inhibitor of Factor VIIa complexed with tissue factor that recently completed a Phase II study in pancreatic cancer; and an unnamed Btk inhibitor in Phase I testing to treat autoimmune diseases.

Novo Nordisk A/S has rights to use PCI-27483 as an excipient for one of its products in a non-oncologic indication under a 2012 deal. AbbVie said it would keep Pharmacyclics as a stand-alone “center of excellence.”

FITTING IN
Potential upsides for Imbruvica include combinations with other oral hematologic agents in AbbVie’s pipeline and expansion into autoimmune disease.

Imbruvica brings a third mechanism of action into AbbVie’s late-stage stable of oral lymphoma therapies. Duvelisib (IPZ-I45) and venetoclax (ABT-199) are in separate Phase III trials to treat CLL and in earlier trials for other hematologic malignancies.

Duvelisib is an oral inhibitor of phosphoinositide 3-kinase (PI3K) delta and gamma. AbbVie is co-developing and co-commercializing the compound with Infinity Pharmaceuticals Inc.

Venetoclax is a small molecule B cell lymphoma 2 (BCL-2; BCL2) inhibitor that AbbVie is co-developing with Roche.

On the March 5 call, AbbVie pegged both duvelisib and venetoclax as candidates for Imbruvica combinations. The pharma is already studying venetoclax in a Phase II study in patients with relapsed or refractory CLL after receiving Imbruvica or Zydelig idelalisib. Zydeig is a PI3K inhibitor marketed by Gilead Sciences Inc. to treat CLL, follicular lymphoma and small lymphocytic lymphoma (SLL).

The transaction also gives AbbVie a ready-made commercial force for hematologic oncology. Pharmacyclics and Jansen co-promote Imbruvica in the U.S., with Pharmacyclics taking the lead.

“ON ONE HAND THEY’RE BUYING ONLY HALF A DRUG, BUT ON THE OTHER HAND THEY’RE BUYING A CANCER PIPELINE.”

JONATHAN GERTLER, BACK BAY LIFE SCIENCE ADVISORS

Chief Commercial Officer Shawn Cline Tomasello previously was president of the Americas, hematology and oncology at Celgene Corp, and before that she was national director of hematology for Rituxan rituximab at Genentech Inc.

THE PLACES YOU’LL GO
AbbVie will have a head start on building its franchise thanks to Pharmacyclics’ previous plans to add one or more new indications to Imbruvica’s label each year. The drug is in 58 clinical studies, including 13 Phase III trials.

Several of the Phase IIIIs will support moving Imbruvica up lines of treatment. The open-label RESONATE-2 trial is testing Imbruvica vs. chlorambucil in CLL and SLL patients who are over 65; results are expected in mid-2015. The SHINE trial is testing the combination of Imbruvica, Treanda bendamustine and Rituxan vs. Treanda plus Rituxan in patients with newly diagnosed MCL, with results expected in 2018.

Teva Pharmaceutical Industries Ltd. markets Treanda to treat several hematologic cancers.

AbbVie won’t have to wait long for readouts on new hematologic oncology indications. Pharmacyclics’ Phase II trial in follicular lymphoma and Phase 1 trial in multiple myeloma (MM) are expected to report data this year (see “Imbruvica’s 2015 Readouts”).

IMBRUVICA’S 2015 READOUTS

On its 4Q14 earnings call last month, Pharmacyclics Inc. (NASDAQ:PCYC) highlighted five of 58 ongoing clinical trials of Imbruvica ibrutinib as “forward-looking value drivers” in hematology that will read out in 2015. These studies support new combinations, earlier lines of therapy and/or new hematologic oncology indications for Imbruvica. Pharmacyclics and partner Johnson & Johnson (NYSE:JNJ) market Imbruvica in the U.S. as monotherapy to treat mantle cell lymphoma (MCL) in patients who have received at least one prior treatment, chronic lymphocytic leukemia (CLL) in patients who have received at least one prior treatment or have the 17p deletion, and Waldenstrom’s macroglobulinemia (WM).

(A) Teva Pharmaceutical Industries Ltd. (NYSE:TEVA) markets Treanda bendamustine and Roche (SIX:ROG; OTCQX:RHHBY) and its Genentech Inc. unit market Rituxan rituximab; (B) Pfizer Inc. (NYSE:PFE) markets Torisel temsirolimus; (C) Amgen Inc. (NASDAQ:AMGN) markets Kyprolis carfilzomib; Sources: Pharmacyclics and AbbVie investor presentations, ClinicalTrials.gov

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On Pharmacyclics’ 4Q14 earnings call, Chairman and CEO Robert Duggan said Imbruvica has also shown preclinical evidence of efficacy in lung, breast, colon and pancreatic cancers. Pharmacyclics and the University of Texas MD Anderson Cancer Center plan to begin an investigator-sponsored Phase I/II study of Imbruvica in patients with non-small cell lung cancer (NSCLC) this year.

Imbruvica’s potential indications outside of oncology include those associated with B cell pathologies, such as rheumatoid arthritis (RA), lupus and GvHD.

Imbruvica is in Phase I to treat GvHD, with results due late this year.

SPARSE FIELD

Imbruvica’s ability to grow sales will also depend on its ability to defend against upcoming challengers in blood cancers; however, the molecule has a sizable head start over other Btk inhibitors, at least three of which are in the clinic for cancer indications.

Last December, Ono Pharmaceutical Co. Ltd. granted exclusive rights to Gilead outside of certain Asian countries to GS-4059 (ONO-4059), a Btk inhibitor that has completed Phase I testing to treat CLL and non-Hodgkin’s lymphoma (NHL). Gilead spokesperson Nathan Kaiser said the company has not given guidance on when Phase II trials may begin.

Acerta Pharma B.V. is testing ACP-196 in Phase I to treat CLL and SLL.

And in August, BeiGene Co. Ltd. began a Phase I study of BGB-3111 in patients with B cell malignancies.

A fourth potential competitor in cancer has fallen by the wayside. According to spokesperson Greg Geissman, Celgene had been studying spebrutinib (CC-292) in Phase II testing to treat CLL, but stopped developing it in oncology after determining that “the current clinical profile does not support the pursuit of a large Phase III CLL trial.” CC-292 is still in Phase II testing to treat RA.

AbbVie’s acquisition of Pharmacyclics is slated to close in 2Q15.

COMPANIES AND INSTITUTIONS MENTIONED

AbbVie Inc. (NYSE:ABBV), Chicago, Ill.
Acerta Pharma B.V., Oss, the Netherlands
Back Bay Life Science Advisors, Boston, Mass.
BeiGene Co. Ltd., Beijing, China
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Genentech Inc., South San Francisco, Calif.
Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Novo Nordisk A/S (CSE:NNO; NYSE:NVO), Bagsvaerd, Denmark
Ono Pharmaceutical Co. Ltd. (Tokyo:4528), Osaka, Japan
Pharmacyclics Inc. (NASDAQ:PCYC), Sunnyvale, Calif.
Shire plc (LSE:SHP; NASDAQ:SHPG), Dublin, Ireland
Teva Pharmaceutical Industries Ltd. (NYSE:TEVA), Petah Tikva, Israel
University of Texas MD Anderson Cancer Center, Houston, Texas

REFERENCES

McCallister, E. “AbbVie’s plan B.” BioCentury (2014)
HARNESSING DATA FOR AD

BY JENNIFER RHODES, STAFF WRITER

A new initiative from the Global CEO Initiative on Alzheimer’s Disease and Optum Labs aims to harness big data sets and analysis tools to better identify patients at risk for developing Alzheimer’s disease. The partners expect AD stakeholders will use the data and tools to tailor patient care and save the healthcare system money.

A not-for-profit industry coalition focused on AD research, the Global CEO Initiative on Alzheimer’s Disease (CEOi) is leading the Big Data Research Initiative to Fight Alzheimer’s Disease, which was launched last month to provide resources to enable industry, academia and government agencies to use big data to develop a better understanding of who will develop AD, and when; how quickly a person’s AD will progress; and how best to deliver care.

“You can see a wide variety of potentially quite interesting things happening to people on the path to Alzheimer’s and people not on the path to Alzheimer’s” by looking through claims data, electronic health records and consumer data, said George Vradenburg, founder and chairman of not-for-profit advocacy group USAgainstAlzheimer’s. Vradenburg and USAgainstAlzheimer’s convened CEOi.

CEOi’s effort is the latest big data initiative looking to tackle AD. The latest results from another initiative, NIH’s Accelerating Medicine Partnership for Alzheimer’s Disease (AMP-AD), were made available on March 4 (see “Amassing AD Data,” page 12).

PROVIDING POWER

It was Optum Labs’ volume of data combined with its analysis tools to sort and analyze those data that attracted CEOi, according to Vradenburg.

The Mayo Clinic and the Optum IT healthcare services business of UnitedHealth Group Inc. launched Optum Labs in 2013 to evaluate data from insurance claims and clinical records. Optum Labs has a database of 161 million records of claims data going back 20 years. Through UnitedHealth’s 2013 acquisition of healthcare analytics company Humedica Inc., Optum Labs also has electronic health record (EHR) data covering 50 million lives over three to seven years. All of the data are de-identified.

Optum Labs CEO Paul Bleicher said the unit has about the same amount of data on consumers as it has for EHRs. He declined to comment on where the consumer data come from, but said it “really gives you more of a picture of the person and of the aspects of their lives that can be usefully applied to predictive models.”

For instance, he said factoring in data on a person’s living environment, such as whether that individual lives alone, increases the accuracy of predicting whether that person will develop congestive heart failure.

“This kind of consumer data becomes most useful when it becomes linked to the claims data and the clinical data, when you understand a person’s path through the clinical world and the rest of their life,” Bleicher said.

Optum Labs provides selected data to researchers in what it calls a sandbox along with proprietary analysis tools that are broadly available like statistical analysis program R.

A sandbox is a virtual desktop onto which Optum Labs can allow access to only the data appropriate for a particular project. The sandbox allows researchers to work with the data and all of Optum Labs’ tools regardless of where they are; the data still reside on the unit’s servers.

Bleicher said Optum Labs has a “very sophisticated data visualization” tool that gives researchers a sense of the size of a particular population and an idea of a potential signal as a starting point.

Another tool allows a researcher to compare selected groups of patients with particular characteristics to matched controls — for instance, by comparing other disease diagnoses or procedures in the populations — over time.

Optum Labs analysts help guide researchers, to point them to particular data and help formulate queries and research questions. While the unit has analysts on its staff, Bleicher noted Optum Labs does not actually do analysis or work for projects.

“Our role is to convene and to get our partners to work on these projects,” he said. “We help the organizations to bring together their thinking to learn about big data and how they can use big data and to identify the right academics and life sciences organizations that can work together to create opportunities around the discussion and reporting of results.”

THE AD PROJECT

Vradenburg said it took Optum Labs about a half hour to call up the records of 100,000 AD patients and 100,000 matched controls and pull up claims data and EHRs for patients dating back one, three, five and 10 years.

Based on that cursory search, Vradenburg said there was a historical difference in falls that could be a potential behavioral marker for AD.

“IF YOU CAN IDENTIFY AND PREDICT THOSE PATIENTS, YOU CAN INTERVENE IN DIFFERENT WAYS AND IMPROVE OUTCOMES AND REDUCE COSTS.”

PAUL BLEICHER, OPTUM LABS
Identifying these sorts of markers of disease and progression are key aspects of the initiative, he said.

“Can we find a set of indicators that suggests a greater likelihood of a person going to get a diagnosis of AD? Can we find predictors of who is a fast progressor and who is a slow progressor?” asked Vradenburg. “It may very well be that your drug works on some subsets of the population and not others, or the power of your drug is masked because you don’t know if the participants in your trial are fast or slow progressors. Pharma companies will find that of interest.”

“It’s pretty obvious what we call Alzheimer’s today is probably many diseases,” said Bleicher.

Vradenburg said CEOi and Optum Labs also expect the data can be sliced and diced to answer questions on care for AD patients.

“Can we find out what kinds of personalized care interventions for individuals are better than others, based on the person’s history and preferences, to determine how best to personalize care intervention?” he said. “Insurance companies may be interested if we can maintain a person’s functional abilities longer than we otherwise might because we understand what kind of care intervention is best.”

Knowing the best way to treat a patient based on characteristics and health history may reduce doctor visits and delay movement into a residential treatment facility, for instance. “Payers are interested in potential interventions that maintain function of an individual as long as possible so healthcare costs are reduced,” said Vradenburg.

It is this ability to potentially improve care and generate cost savings that is important to Optum Labs, said Bleicher. “If you can identify and predict those patients you can intervene in different ways and improve outcomes and reduce costs. That’s one of the things we’re really focused on.”

The Optum Labs database does not include genomic or imaging data, and Bleicher said the unit does not have plans to add these, in part because of enhanced privacy concerns and because the costs to store and maintain these types of data are non-trivial.

He said the unit will likely partner with genomics institutes down the road.

“We could potentially link data with a genomic database and then we can send them information on ‘here’s the patients in your database who don’t have the disease, here are the patients that do have the disease,’ and they can send us back the data of what percentage have this SNP,” said Bleicher.

### AMASSING AD DATA

Beyond the Big Data Research Initiative to Fight Alzheimer’s Disease, at least two other big data initiatives have sought to identify biomarkers and understand progression of AD: the Accelerating Medicines Partnership for Alzheimer’s Disease (AMP-AD) and the Alzheimer’s Disease Big Data DREAM Challenge #1.

On March 4, Sage Bionetworks made available the first results from AMP-AD’s Target Discovery and Preclinical Validation Project. In that effort, groups with five-year NIH grants are applying systems and network biology to -omics data to discover novel targets and evaluate their druggability, and to gain an understanding of the gene, protein and metabolic networks within which these targets operate.

The researchers are analyzing clinical and pathological data from more than 2,000 human brains at all stages of AD. The results are then made publicly available online at the AMP-AD Knowledge Portal, which launched this month.

The data made available by Sage, which facilitates data sharing for the project, include brain samples from different regions with corresponding demographic and neuropathological data and gene co-expression network analyses.

A second AMP-AD project is exploring the utility of tau imaging and novel fluid biomarkers for tracking responsiveness to treatment and disease progression.

NIH’s AMP is a precompetitive partnership that involves not-for-profits, 10 pharma companies and FDA and is focused on discovering novel targets and biomarkers for AD, Type II diabetes and autoimmune diseases.

USAgainstAlzheimer’s is involved in AMP-AD, along with four other not-for-profits and four pharma.

The other big data initiative for AD, the DREAM Challenge, was a competition organized by the Global CEO Initiative on Alzheimer’s Disease (CEOi), Sage and DREAM Challenges, an initiative founded in 2006 to organize computational challenges around fundamental systems biology questions.

The AD challenge, which closed in October, aimed to predict biomarkers for early AD-related cognitive decline.

Academic teams had access to imaging and clinical data along with whole genome sequencing and cognitive tests for cohorts of individuals who are healthy and have aged normally, who suffer from mild-cognitive impairment or who have AD.

The challenge comprised three subchallenges: predict the change in cognitive scores 24 months after initial assessment; predict the set of cognitively normal individuals whose biomarkers suggest amyloid perturbation; and classify individuals into diagnostic groups using MRI.

Academic teams from the University of Michigan and the Karolinska Institute were the top performers on the first subchallenge; while the Michigan team was the top performer on the third. In the second, no team was able to develop a model that performed significantly better than random.

— JENNIFER RHODES
“We don’t ever have to hold the genomic data, and they don’t have to hold the clinical data,” he added.

Optum Labs does not currently have clinical data, but the unit is looking to add data from disease registries.

**WHAT’S NEXT**

CEOi has undisclosed seed funding for the Big Data Research Initiative to Fight Alzheimer’s Disease, but is looking to partners to fund the initiative and individual research projects. Vradenburg said CEOi and Optum Labs are talking with potential partners for research projects; he declined to comment on a timeline for the first project.

The initiative will be open to all stakeholders, but Vradenburg noted CEOi will be in contact first with its member organizations: AC Immune S.A., Banner Health, Bank of America, Eli Lilly and Co., General Electric Co.’s GE Healthcare unit, Home Instead Inc., Johnson & Johnson’s Janssen Research & Development LLC unit, Merck & Co. Inc., Nestle S.A.’s Nestle Health Science unit, Pfizer Inc., Roche, Sanofi and Takeda Pharmaceutical Co. Ltd.

Optum Labs also has over 20 collaborating partners who may be involved in projects.

The partners include AARP and Harvard Medical School’s Department of Health Care Policy and industry members Boston Scientific Corp., Merck, Novartis AG, Pfizer and respiratory device play ResMed Inc.

“The idea is that we’re all stakeholders in healthcare, and we all approach the same problems in different ways,” Bleicher said. ■
**GENOMIC-LINKED OUTCOMES**

BY STEPHEN HANSEN, ASSOCIATE EDITOR

14M Genomics Ltd. aims to improve the prognostic value of cancer genome profiling by linking a patient’s genomic signature with clinical outcomes compiled from large data sets.

14MG’s tests use next-generation sequencing combined with algorithms to map a patient’s cancer genome and identify mutations. The results of the test are intended to inform doctors which genetic mutations are driving a patient’s cancer and which therapy will provide the best outcome based on a correlation between the genomic signature and clinical data.

The increased availability and use of next generation sequencing is making tumor profiling more common. But according to co-founder Ultan McDermott, such information provides doctors with only half the story: “A lot of the sequencing companies provide a list of mutations with some annotation as to what they mean clinically, but these rely on historical literature,” McDermott told BioCentury. “They are sequencing the samples, but unless you do the next step and match those with the clinical outcomes, then you end up with a lot of data which is very difficult to comprehend.”

McDermott is group leader at the Wellcome Trust Sanger Institute and an oncologist at Addenbrooke’s Hospital.

14MG is the result of over 12 years of work on the Sanger Institute Cancer Genome Project. Executive Chairman Andrew Sandham said 14MG licensed bioinformatics and algorithms from Sanger to analyze the mutations, while the company developed its own panel of 400 cancer mutations for solid tumors and 350 mutations for hematological malignancies.

14MG has access to Sanger’s sequencing infrastructure, which can process up to 30,000 tumor samples a month.

Most cancers are driven by a mix of mutations in 10-20 genes that may act together to drive a cancer. According to Sandham, creating a reference database linking complex genomic signatures with clinical outcomes is the only way to know a patient’s prognosis and identify the best treatment.

Wellcome is helping 14MG gain access to both retrospective and prospective data sets to build a reference database.

In February, 14MG partnered with the UK’s Haematological Malignancy Research Network to retrospectively sequence the cancer genomes of 20,000 patients. The signatures will be correlated with each patient’s clinical outcome to create a database for 14MG’s hematological malignancies test.

In the commercial setting, a patient’s cancer genome can be sequenced and compared with the database to identify which treatments resulted in the best clinical outcomes for patients with the same signature.

Sandham said the data’s quality will be much higher than reference literature because the study investigators documented the outcomes to GCP standards over a 15-year period and received patient consent to use the data.

McDermott noted that other molecular profiling tests can produce results where a mutation has an unknown significance. If the underlying data set is large enough, he said, 14MG may be able to eliminate many variations of unknown significance, giving oncologists more actionable information.

Sandham said 14MG is working to gain access to other large cancer studies funded by Wellcome Trust that would provide similar data sets in solid tumors.

Nevertheless, he noted that retrospective analysis only links genomic profiles to existing therapies. Prospective studies incorporating 14MG’s genomic profiling test into clinical studies would all the reference data set to include clinical outcomes from late-stage therapies that, if successful, could become the next wave of cancer products.

Last week, 14MG announced its first deal for prospective studies. It will sequence the cancer genomes of patients enrolling in the European Organisation for Research and Treatment of Cancer’s Screening Patients for Efficient Clinical Trial Access (SPECTA) program.

Sandham said SPECTA expects to enroll about 2,000 patients annually with solid tumors. The program will use the genomic profile information to enroll patients in the most appropriate clinical trials, and 14MG will have access to the subsequent outcomes for use in its solid tumor reference data set.

Fellow pharmacogenetics company Foundation Medicine Inc. has also started adding to its data set through prospective studies via its deal with Flatiron Health Inc., which seeks to integrate clinical treatment and outcomes data with genomic profiling data.

Sandham, who is also a partner at Syncona Partners, said the firm plans to keep 14MG private, as building the reference database for its cancer genome profiling test will take time and “we want to make sure we don’t get forced to be driven by financial numbers.” Syncona is a Wellcome subsidiary.

**COMPANIES AND INSTITUTIONS MENTIONED**

European Organisation for Research and Treatment of Cancer, (EORTC), Brussels, Belgium

Flatiron Health Inc., New York, N.Y.

Foundation Medicine Inc. (NASDAQ:FMI), Cambridge, Mass.

14M Genomics Ltd., Hinxton, U.K.

Wellcome Trust, London, U.K.
CHIASMA’S PRIVATE DECISION

Chiasma Inc. profiles as a potential IPO candidate with a late-stage asset on the verge of registration. But MPM Capital’s Todd Foley told BioCentury that the recent unexpected return of commercial rights for its octreotide acetate to treat acromegaly meant the timing wasn’t right.

Instead, Chiasma’s investors opted for an additional venture financing, putting in $70 million in an oversubscribed series E round led by an undisclosed crossover fund. New investors Rock Springs Capital and Sofinnova Ventures participated, along with existing investors MPM, F2 Capital, 7 Med Health Ventures, Abingworth and Arch Venture Partners.

Foley said the cash will primarily go toward building Chiasma’s regulatory and commercialization capabilities, as the company expects to submit an NDA for octreotide by mid-year under the section 505(b)(2) pathway. The compound is an oral formulation of a somatostatin analog.

Chiasma had been expecting partner Roche (SIX:ROG; OTCQX:RHHBY) to handle the regulatory filings and commercialization under a February 2013 deal. But the pharma returned rights last July after reviewing octreotide’s Phase III data and feedback from regulators.

In January, Chiasma CEO Roni Mamluk said Roche’s decision was “sudden and unexpected,” given the results of the Phase III trial, which showed that in 151 acromegaly patients, 98 (65%) achieved the primary endpoint of hormonal control at final assessment of a seven-month fixed-dose period.

Although Mamluk declined to disclose specifics, she told BioCentury that Chiasma did not share Roche’s “subjective interpretation” of the evidence and regulatory feedback.

Foley told BioCentury that Chiasma investors are comfortable with the regulatory prospects for octreotide as “many people have voted with their feet and pocketbooks to join Chiasma in the past few months.”

Since Chiasma regained rights to the product, MPM Managing Director Gary Patou became senior medical advisor; he also serves as CMO at Pacira Pharmaceuticals Inc. (NASDAQ:PCRX). Pacira Chairman, President and CEO David Stack became Chiasma’s chairman. And John Scarlett became an independent board member; he is president and CEO of Geron Corp. and was previously CEO at Proteolix Inc. and Tericica Inc.

MPM is one of Chiasma’s largest shareholders, with about a 30% stake.

— Stephen Hansen

MRNA FOR THE DEVELOPING WORLD

The Bill & Melinda Gates Foundation and CureVac GmbH found a win-win deal that allows Gates to fund development of vaccines that meet its requirements for developing low cost vaccines to prevent infectious diseases in the developing world, while CureVac gets a manufacturing facility to meet its R&D and commercial needs.

On March 5, the charity made a $52 million equity investment in CureVac and partnered with the mRNA company to provide an undisclosed amount of non-dilutive funding to develop mRNA-based prophylactic vaccines against infectious diseases prevalent in the developing world. In parallel, CureVac’s major shareholder dievini Hopp Biotech invested an additional $24 million.

According to Andrew Farnum, deputy director of program related investments at Gates, CureVac’s RNAactive mRNA vaccine technology provides three key advantages over traditional vaccine development approaches.
First, it allows for faster vaccine development, as the RNA-based approach allows “you to go from an antigen sequence to an actual GMP product that is ready for clinical testing in a matter of weeks, rather than months or years with a traditional vaccine manufacturing process,” he said.

Second, Farnum and Ingmar Hoerr, co-founder and CEO of CureVac, told BioCentury that mRNA-based vaccines have a very low cost of goods. Farnum said this was critical because “we did a lot of analysis, and we think we can get the cost down to the level where it can be affordable for poor populations.”

Third, and most critical for delivering vaccines to the developing world, RNActive vaccines are thermostable. “This will be an absolute breakthrough,” Farnum said, as it will allow vaccines to be much more broadly available without the need for cold chain storage.

According to Hoerr, the vaccines are stable for more than a year at room temperature.

Farnum added that the RNActive technology also should be applicable to a long list of infectious diseases for which the foundation is trying to develop vaccines. The first two disclosed programs are against rotavirus and HIV, both of which are in preclinical development.

Hoerr said most of the Gates investment will go toward the building of a GMP facility that will be able to manufacture up to 30 million doses of mRNA-based vaccines a year. He said about 25% of the facility is dedicated to the Gates program, leaving the other 75% to support CureVac’s in-house and partnered programs.

— Stephen Hansen

**AURA FINDS THE RIGHT MIX**

Aura Biosciences Inc. has been developing its viral nanoparticle technology without the backing of institutional investors since 2009. New VC investors told BioCentury that Aura’s work over the past 12–24 months to find the right indication and companion drug for the platform were enough to attract their investment.

Aura raised $21 million in a series B round early this month led by new investor Advent Life Sciences. New investors Chiesi Ventures, Ysis Capital and Alexandria Venture Investments also participated, along with existing investors Li-Cor Biosciences and Henri Termeer, former chairman, president and CEO of Genzyme Corp.

The company had previously raised $11.1 million over three rounds.

Aura expects lead program AU011 to enter the clinic by year end to treat rare ocular cancers. The compound comprises tumor-targeting viral nanoparticles conjugated to Li-Cor’s IRDye 700DX, a laser-activated cytotoxin.

According to Advent’s Dale Pfost, Aura really became attractive after it honed in on the best application for its technology.

In 2011, Aura told BioCentury it was developing the viral nanoparticles for siRNA delivery in HPV-related cancers or for imaging tumors using fluorescent proteins (see BioCentury, Nov. 14, 2011). Aura subsequently dropped the programs and is now focused on AU011.
Pfost said Aura found the best application for the technology about two years ago when it decided to pursue rare ocular cancers, where the standard of care is surgical removal of the eye.

“They found the right combination of the indication as well as the endpoints for those indications, plus the right nanoparticle and active agent,” he said.

Pfost said the new cash should get AU011 through Phase II testing.

The deal marks the first investment from Chiesi Ventures. Managed by A.M. Pappas and Associates and launched by Orphan Drug company Chiesi Farmaceutici S.p.A., the strategic venture fund is focused on rare diseases (see BioCentury, Sept. 8, 2014).

Art Pappas told BioCentury Chiesi is not disclosing how much the fund has raised, but he noted Aura is a prime example of the types of investments Chiesi would be making. He said additional deals should be expected in the coming months.

— Stephen Hansen

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**CLARIFICATION**

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

Regeneron Pharmaceuticals Inc. (NASDAQ:REGN), Tarrytown, N.Y.

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

Business: Endocrine/metabolic

PCSK9 inhibitors Praluent alirocumab from Sanofi and Regeneron and evolocumab from Sanofi have different dosage strengths; however, both compounds were tested at bi-weekly and once-monthly intervals in clinical trials. The March 9 BioCentury misstated the dosing regimen.
**Analyst picks & changes**

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Peaker also removed his $14 target after AcelRx said it will delay the resubmission of an NDA for Zalviso sufentanil sublingual tablet system to treat acute pain. According to AcelRx, FDA requested an additional clinical trial to “assess the risk of inadvertent dispensing and overall risk of dispensing failures.” The company had hoped to submit the NDA this quarter. Peaker lowered his peak sales estimate for the preprogrammed, handheld device that delivers a sublingual formulation of sufentanil to about $719M in 2027.

Amin also lowered his target to $6 from $12. He thinks “it’s unclear how one could design a clinical trial to assess the risk of dispensing failures” and pushed back his Zalviso launch estimate to 2018 from 2016. He also lowered his peak risk-adjusted sales to $465M from $512M by 2031.

Corso also lowered his target to $5.59 from $14 on the Zalviso delay. He lowered his 2020 Zalviso revenue estimate to $263M from $395M.

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</tbody>
</table>

Butt also raised his target to $10 from $2.50 after the company announced plans to raise up to $52.8M in a private placement primarily to support the REDUCE-IT cardiovascular outcomes study of hypertriglyceridemia drug Vascepa icosapent ethyl. He maintains that the trial “is the ultimate value-driver” for the >96% pure ethyl ester of eicosapentaenoic acid (ethyl-EPA) supporting a launch in patients with very high triglycerides. Fein expects a launch for the indication in 2018.

<table>
<thead>
<tr>
<th>Company</th>
<th>Bank</th>
<th>Analyst</th>
<th>Coverage</th>
<th>Opinion</th>
<th>Wk chg</th>
<th>3/13 cls</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcelRx Pharmaceuticals Inc. (NASDAQ:ACRX)</td>
<td>Piper Jaffray</td>
<td>Charles Duncan</td>
<td>Upgrade</td>
<td>Overweight (from neutral)</td>
<td>17%</td>
<td>$4.00</td>
</tr>
</tbody>
</table>

Duncan also raised his target to $9 from $2.50 after interviewing prescribers of Korlym mifepristone. He thinks there is “under-recognized” value from the potential in cancer, broader use in adrenal or pituitary surgery and increasingly visible second generation compounds. Duncan added triple-negative breast cancer to his valuation with net U.S. sales of $360M in 2024. Korlym is in Phase II testing for the indication and is already marketed to treat Cushing’s syndrome.

<table>
<thead>
<tr>
<th>Company</th>
<th>Bank</th>
<th>Analyst</th>
<th>Coverage</th>
<th>Opinion</th>
<th>Wk chg</th>
<th>3/13 cls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrexon Corp. (NYSE:XON)</td>
<td>Mizuho</td>
<td>Peter Lawson</td>
<td>Downgrade</td>
<td>Neutral (from buy)</td>
<td>-7%</td>
<td>$46.49</td>
</tr>
</tbody>
</table>

Lawson downgraded on valuation as Intrexon stock neared his $50 target. He said he needs to see additional clinical data from partnerships to “get comfortable with the upside.” In January, Intrexon and partner Ziopharm Oncology Inc. (NASDAQ:ZIOP) licensed chimeric antigen receptor (CAR) T cell technology from the University of Texas MD Anderson Cancer Center. The companies said the technology will allow them to bring as many as five cancer therapies into the clinic this year.

<table>
<thead>
<tr>
<th>Company</th>
<th>Bank</th>
<th>Analyst</th>
<th>Coverage</th>
<th>Opinion</th>
<th>Wk chg</th>
<th>3/13 cls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pernix Therapeutics Holdings Inc. (NASDAQ:PXTX)</td>
<td>Cantor Fitzgerald</td>
<td>Irina Rivkind Koffler</td>
<td>Downgrade</td>
<td>Hold (from buy)</td>
<td>-15%</td>
<td>$10.07</td>
</tr>
</tbody>
</table>

Koffler also lowered her target to $11 from $12 after Pernix announced that it is purchasing the Zohydro ER analogic franchise from Zogenix Inc. (NASDAQ:ZGNX) for $100M up front and up to $283.5M in milestones. Koffler is concerned about the commercial execution risk of Zohydro ER and seeks to “wait and see” how Pernix manages this “aggressive transformational pain deal.” While still a potentially attractive alternative option for patients, Koffler worries that Zohydro ER’s abuse resistant label may be less competitive than that of Hyosingla ER from Purdue Pharma L.P.

<table>
<thead>
<tr>
<th>Company</th>
<th>Bank</th>
<th>Analyst</th>
<th>Coverage</th>
<th>Opinion</th>
<th>Wk chg</th>
<th>3/13 cls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziopharm Oncology Inc. (NASDAQ:ZIOP)</td>
<td>Mizuho</td>
<td>Peter Lawson</td>
<td>Downgrade</td>
<td>Neutral (from buy)</td>
<td>0%</td>
<td>$13.52</td>
</tr>
</tbody>
</table>

Lawson downgraded on valuation. He said data from Ad-IL-12 has been “modest,” and he needs to see more “encouraging” data from the compound or Ziopharm’s chimeric antigen receptor (CAR) T cell therapy program to keep up with competitors that have “more advanced pipelines, more clinical data and richer catalyst lists.” The DNA vector that contains an inducible promoter to control expression of the IL-12 gene is in Phase II testing to treat breast cancer and Phase I/II testing to treat melanoma. In January, Ziopharm and partner Intrexon Corp. (NYSE:XON) licensed CAR T cell technology from the University of Texas MD Anderson Cancer Center.

<table>
<thead>
<tr>
<th>Company</th>
<th>Bank</th>
<th>Analyst</th>
<th>Coverage</th>
<th>Opinion</th>
<th>Wk chg</th>
<th>3/13 cls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zogenix Inc. (NASDAQ:ZGNX)</td>
<td>William Blair</td>
<td>Tim Lugo</td>
<td>Downgrade</td>
<td>Market perform (from outperform)</td>
<td>-3%</td>
<td>$1.30</td>
</tr>
</tbody>
</table>

Lugo also removed his $2.25 target after Zogenix announced the sale of its Zohydro ER analogic franchise to Pernix Therapeutics Holdings Inc. (NASDAQ:PXTX). Lugo believes the “disappointing” sale of the company’s sole commercial asset represents a “significant transition” for Zogenix into a late-stage CNS development company. Combined with a lack of Phase III candidates, Lugo thinks the sale of Zohydro ER will cap share performance in the near term.
**PRICE GAINS**

Stocks with greatest % price increase in the week ended 3/13. (Priced above $2; 5,000 minimum share volume)

<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>Recro</td>
<td>REPH</td>
<td>5.950</td>
<td>2.660</td>
<td>81%</td>
<td>21769</td>
</tr>
<tr>
<td>Mela Sciences</td>
<td>MELA</td>
<td>3.040</td>
<td>1.208</td>
<td>66%</td>
<td>173530</td>
</tr>
<tr>
<td>Amarin</td>
<td>AMRN</td>
<td>2.900</td>
<td>1.120</td>
<td>63%</td>
<td>720188</td>
</tr>
<tr>
<td>Asterias</td>
<td>AST</td>
<td>7.750</td>
<td>2.990</td>
<td>63%</td>
<td>17701</td>
</tr>
<tr>
<td>Immunicum</td>
<td>IMMU</td>
<td>SEK40.000</td>
<td>SEK12.800</td>
<td>47%</td>
<td>16355</td>
</tr>
<tr>
<td>Lion Biotechnologies</td>
<td>LBIO</td>
<td>13.020</td>
<td>4.120</td>
<td>46%</td>
<td>45667</td>
</tr>
<tr>
<td>Ampio</td>
<td>AMPE</td>
<td>7.980</td>
<td>2.100</td>
<td>36%</td>
<td>92919</td>
</tr>
<tr>
<td>Relmada</td>
<td>RLMD</td>
<td>3.550</td>
<td>0.901</td>
<td>34%</td>
<td>21272</td>
</tr>
<tr>
<td>Verastem</td>
<td>VSTM</td>
<td>10.760</td>
<td>2.430</td>
<td>29%</td>
<td>41396</td>
</tr>
<tr>
<td>ContraFect</td>
<td>CFRX</td>
<td>5.800</td>
<td>1.190</td>
<td>26%</td>
<td>9961</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>AcelRx</td>
<td>ACRX</td>
<td>4.055</td>
<td>-4.685</td>
<td>-54%</td>
<td>134394</td>
</tr>
<tr>
<td>R-Tech Ueno</td>
<td>4573</td>
<td>¥1366.000</td>
<td>¥934.000</td>
<td>-41%</td>
<td>35815</td>
</tr>
<tr>
<td>Neuralstem</td>
<td>CUR</td>
<td>2.560</td>
<td>-1.230</td>
<td>-32%</td>
<td>203682</td>
</tr>
<tr>
<td>ThromboGenics</td>
<td>THR</td>
<td>€6.185</td>
<td>-1.729</td>
<td>-22%</td>
<td>11999</td>
</tr>
<tr>
<td>Tracon</td>
<td>TCON</td>
<td>13.750</td>
<td>-€3.820</td>
<td>-22%</td>
<td>5367</td>
</tr>
<tr>
<td>Adamis</td>
<td>ADMP</td>
<td>5.540</td>
<td>-1.260</td>
<td>-19%</td>
<td>9307</td>
</tr>
<tr>
<td>Cancer Genetics</td>
<td>CGIX</td>
<td>7.030</td>
<td>-1.580</td>
<td>-18%</td>
<td>5389</td>
</tr>
<tr>
<td>Lipocine</td>
<td>LPCN</td>
<td>6.620</td>
<td>-1.290</td>
<td>-16%</td>
<td>4950</td>
</tr>
<tr>
<td>Bellerophon Therapeutics</td>
<td>LBPH</td>
<td>9.750</td>
<td>-1.890</td>
<td>-16%</td>
<td>687</td>
</tr>
<tr>
<td>Organovo Holdings</td>
<td>ONVO</td>
<td>7.750</td>
<td>-1.460</td>
<td>-16%</td>
<td>3046</td>
</tr>
<tr>
<td>Apricus Biosciences</td>
<td>APRI</td>
<td>2.070</td>
<td>-0.390</td>
<td>-16%</td>
<td>17383</td>
</tr>
<tr>
<td>ADMA</td>
<td>ADMA</td>
<td>4.055</td>
<td>-4.685</td>
<td>-54%</td>
<td>134394</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>Mela Sciences</td>
<td>MELA</td>
<td>173530</td>
<td>8869</td>
<td>3.040</td>
<td>1.208</td>
</tr>
<tr>
<td>Recro</td>
<td>REPH</td>
<td>21769</td>
<td>4389</td>
<td>5.950</td>
<td>2.660</td>
</tr>
<tr>
<td>DNA Chip Research</td>
<td>2397</td>
<td>4352</td>
<td>1443</td>
<td>853.000</td>
<td>33.000</td>
</tr>
<tr>
<td>ProBioDrug</td>
<td>PRO</td>
<td>141</td>
<td>1253</td>
<td>19.210</td>
<td>1.710</td>
</tr>
<tr>
<td>Heat Biologics</td>
<td>HTBX</td>
<td>18776</td>
<td>1024</td>
<td>7.350</td>
<td>0.000</td>
</tr>
<tr>
<td>co.don</td>
<td>CNWK</td>
<td>1019</td>
<td>657</td>
<td>2.450</td>
<td>0.156</td>
</tr>
<tr>
<td>Genecor</td>
<td>GNCA</td>
<td>8795</td>
<td>1543</td>
<td>9.420</td>
<td>0.960</td>
</tr>
<tr>
<td>Skypharma</td>
<td>SKP</td>
<td>27940</td>
<td>514</td>
<td>319.8p</td>
<td>14.8p</td>
</tr>
<tr>
<td>Bellerophon Therapeutics</td>
<td>LBPH</td>
<td>687</td>
<td>1253</td>
<td>9.750</td>
<td>1.890</td>
</tr>
<tr>
<td>Immune Design</td>
<td>IMDZ</td>
<td>7651</td>
<td>498</td>
<td>2.450</td>
<td>0.156</td>
</tr>
</tbody>
</table>

1 Volume is of ADSs (1 ADS = 1 share)

**BIOCENTURY 100 PRICE & VOLUME TREND**

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

**BIOCENTURY LONDON INDEX**

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

**BIOCENTURY 100 INDICATORS**

Week ended 3/13/15

**PRICES**

7149.27 up 2%

**VOLUME**

803.4M shrs dn 7%
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- 78 Preclinical/IND
- 20 Phase I
- 25 Phase II
- 5 Phase III/Registration/Marketed

By popular demand, the Future Leaders Class of 2015 expands to include a new “Next Wave” track featuring 15 early stage, privately held companies hand-picked by BioCentury. The “Next Wave” track promises to showcase platform plays and product companies advancing their assets to the clinic and proof of clinical concept.

BD&L PROFESSIONALS
128 Unpartnered Products in More Than 200 Programs

The Future Leaders Class of 2015 has 94 unpartnered products across the spectrum of development that can help your company achieve its business development goals for this year and beyond, including:

- 78 Preclinical/IND
- 20 Phase I
- 25 Phase II
- 5 Phase III/Registration/Marketed

INVESTMENT PROFESSIONALS
15 Early Stage, Private Companies

By popular demand, the Future Leaders Class of 2015 expands to include a new “Next Wave” track featuring 15 early stage, privately held companies hand-picked by BioCentury. The “Next Wave” track promises to showcase platform plays and product companies advancing their assets to the clinic and proof of clinical concept.

Final Slate of Presenting Companies

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Stock Exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceleron Pharma Inc.</td>
<td>NASDAQ:XLRN</td>
</tr>
<tr>
<td>Actinium Pharmaceuticals Inc.</td>
<td>NYSE:ATNM</td>
</tr>
<tr>
<td>Aduro BioPharma Inc.</td>
<td>NASDAQ:ADXS</td>
</tr>
<tr>
<td>Aerie Pharmaceuticals Inc.</td>
<td>NASDAQ:AERI</td>
</tr>
<tr>
<td>Alnylam Pharmaceuticals Inc.</td>
<td>NASDAQ:ALNY</td>
</tr>
<tr>
<td>Ardeyly Inc.</td>
<td>NASDAQ:ARDX</td>
</tr>
<tr>
<td>arkGen-X B.V.</td>
<td>Euronext:ARGX</td>
</tr>
<tr>
<td>Arko Therapeutics Inc.</td>
<td>NASDAQ:ARGS</td>
</tr>
<tr>
<td>AuraSense Therapeutics LLC</td>
<td></td>
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<tr>
<td>Aveil Biosciences Inc.</td>
<td></td>
</tr>
<tr>
<td>Cara Therapeutics Inc.</td>
<td>NASDAQ:CARA</td>
</tr>
<tr>
<td>Celator Pharmaceuticals Inc.</td>
<td>NASDAQ:CPXX</td>
</tr>
<tr>
<td>Cleave Biosciences Inc.</td>
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<tr>
<td>Cortendo AG</td>
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<tr>
<td>CymaBay Therapeutics Inc.</td>
<td>NASDAQ:CBAY</td>
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<tr>
<td>Deciphera Pharmaceuticals LLC</td>
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<tr>
<td>Dimension Therapeutics</td>
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<tr>
<td>Effector Therapeutics Inc.</td>
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<tr>
<td>Esperion Therapeutics Inc.</td>
<td>NASDAQ:ESPR</td>
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<td>Forward Pharma A/S</td>
<td>NASDAQ:FWP</td>
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<tr>
<td>GeNeuro S.A.</td>
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<tr>
<td>Global Blood Therapeutics Inc.</td>
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<tr>
<td>Helomics Corp.</td>
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<tr>
<td>Kadmon Corp. LLC</td>
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<td>Kolltan Pharmaceuticals Inc.</td>
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<tr>
<td>Lamberts Pharmaceuticals Inc.</td>
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<td>Mannus Pharmaceuticals Inc.</td>
<td>NASDAQ:MRNS</td>
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<tr>
<td>Medgenics Inc.</td>
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<tr>
<td>Metabolic Solutions Development Co.</td>
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<tr>
<td>Naurex Inc.</td>
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<tr>
<td>NeoStem Inc.</td>
<td>NASDAQ:NBS</td>
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<tr>
<td>Opsona Therapeutics Ltd.</td>
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<td>Paratek Pharmaceuticals Inc.</td>
<td>NASDAQ:PRTK</td>
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<td>Protagonist Therapeutics Inc.</td>
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<td>Relmada Therapeutics Inc.</td>
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<td>OTCQB:RESX</td>
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<td>Syndax Pharmaceuticals Inc.</td>
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<td>Syros Pharmaceuticals Inc.</td>
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<td>Taris Biomedical Inc.</td>
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<tr>
<td>Trevena Inc.</td>
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<tr>
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<tr>
<td>VBL Therapeutics Ltd.</td>
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</tr>
<tr>
<td>Voyager Therapeutics Inc.</td>
<td></td>
</tr>
<tr>
<td>Xencor Inc.</td>
<td>NASDAQ:XNCR</td>
</tr>
</tbody>
</table>

“Next Wave” Presenting Companies

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Stock Exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ailea Pharmaceuticals Inc.</td>
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</tr>
<tr>
<td>Aridis Pharmaceuticals LLC</td>
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</tr>
<tr>
<td>ArmaGen Inc.</td>
<td></td>
</tr>
<tr>
<td>Atterocor Inc.</td>
<td></td>
</tr>
<tr>
<td>Blaze Bioscience Inc.</td>
<td></td>
</tr>
<tr>
<td>Cefaron Inc.</td>
<td></td>
</tr>
<tr>
<td>Enterome Bioscience S.A.</td>
<td></td>
</tr>
<tr>
<td>G1 Therapeutics Inc.</td>
<td></td>
</tr>
<tr>
<td>ONL Therapeutics Inc.</td>
<td></td>
</tr>
<tr>
<td>Raze Therapeutics Inc.</td>
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<tr>
<td>Scholar Rock LLC</td>
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<tr>
<td>Second Genome Inc.</td>
<td></td>
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<tr>
<td>TensorVX</td>
<td></td>
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</tbody>
</table>
WHY COME TO ChinaBio® PARTNERING FORUM?

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• Hear from industry experts how to strike deals in China.
• Schedule one-to-one meetings with potential partners in advance online.

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COMPANY NEWS

14M Genomics Ltd., Hinxton, U.K.

European Organization for Research and Treatment of Cancer, Brussels, Belgium

Business: Cancer

14M Genomics and the European Organization for Research and Treatment of Cancer (EORTC) partnered to use genomic diagnostic profiles to facilitate enrollment into clinical trials for cancer. 14M Genomics will conduct genomic variation analysis on newly diagnosed colorectal, thoracic, brain and skin cancer patients as part of the EORTC Screening Patients for Efficient Clinical Trial Access (SPECTA) program. After the testing, the EORTC will connect patients within the SPECTA program to the appropriate clinical trials. EORTC enrolled more than 500 colorectal cancer patients in the SPECTA trial and expects to enroll about 2,000 patients per year in the SPECTA program. The partners did not disclose financial terms.

Anaconda Pharma Ltd., Villejuif, France

Biota Pharmaceuticals Inc. (NASDAQ:BOTA), Alpharetta, Ga.

Business: Infectious

Biota is acquiring Anaconda for $8 million in cash and 3.5 million Biota shares, valued at $8.7 million based on Biota’s close of $2.48 on Feb. 25, before the deal was announced. Anaconda shareholders are eligible for up to $30 million in clinical and regulatory milestones, plus low single-digit royalties.

Anaconda’s AP611074 is an inhibitor of E1 and E2 viral proteins of HPV types 6 and 11 and has completed a Phase Ila trial to treat condyloma. A Phase Ib trial to treat anogenital warts is slated to start next half. The deal is expected to close by the end of April (see BioCentury, Feb. 3, 2014).

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


EKF Diagnostics Holdings plc (LSE:EKF), Penarth, U.K.

Greenville Health System, Greenville, S.C.

Business: Cancer

EKF Diagnostics’ Selah Genomics subsidiary partnered with Greenville Health System, DecisionQ and Becton Dickinson under an 18-month deal to use next-generation sequencing (NGS) and algorithms to improve clinical decisions for colon cancer patients. Selah is contributing its PrecisionPath NGS technology to analyze tumor samples, which will be provided by Greenville’s Institute for Translational Oncology Research. DecisionQ will integrate the data with clinical annotations to create a clinical decisions model. Becton is providing part of the funding in exchange for having the first right to license the technology. Selah expects lung cancer will be the next target indication. The partners are not disclosing financial details.

Covis Pharma S.p.A., Zug, Switzerland

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

Business: Infectious, Cancer, Cardiovascular

Concordia will acquire Covis’ commercial assets, specifically its 18 branded and generic products, for $1.2 billion in cash. Covis
The deal includes Nilandron nilutamide, a testosterone blocker that is marketed to treat prostate cancer; cardiovascular drug Lanoxin digoxin, which is a cardiac glycoside; and Plaquenil hydroxychloroquine, an oral formulation of hydroxychloroquine, which is marketed to treat malaria. Sanofi (Euronext:SAN; NYSE:SNY, Paris, France) granted Covis U.S. rights to commercialize Nilandron and Plaquenil in 2013. GlaxoSmithKline plc (LSE:GSK; NYSE:GSK, London, U.K.) granted Covis U.S. rights to commercialize Lanoxin in 2012. The deal is expected to close next quarter (see BioCentury, Jan. 2, 2012 & April 15, 2013).

Duke University, Durham, N.C.

Annias Immunotherapeutics Inc., Chapel Hill, N.C.

Business: Cancer

Duke granted newco Annias exclusive, worldwide rights to develop and commercialize IP covering immune preconditioning technology and IP targeting cytomegalovirus (CMV) to treat cancer. The preconditioning technology is comprised of administering a tetanus/diphtheria toxoid antigen prior to vaccination with autologous dendritic cells pulsed with human CMV phosphoprotein 65 RNA. Researchers at the university have evaluated the technology in a Phase I/II trial in patients with newly diagnosed glioblastoma multiforme (GBM). This year, Annias plans to start a Phase II trial for the indication. The company said that financial terms are not disclosed.

Epizyme Inc. (NASDAQ:EPZM), Cambridge, Mass.

Eisai Co. Ltd., (Tokyo:4523), Tokyo, Japan

Business: Cancer

Epizyme paid $40 million up front to Eisai to regain worldwide rights, excluding Japan, to EPZ-6438. The selective inhibitor of EZH2 (enhancer of zeste homolog 2) is in Phase I/II testing to treat B cell non-Hodgkin's lymphoma (NHL) and SWI/SNF related matrix associated actin dependent regulator of chromatin subfamily b member 1 (SMARCB1; SNF5; 1N11)-deficient solid tumors (see BioCentury, March 9).

Epizyme plans to start Phase II testing in NHL patients in Europe in 2Q15. Next half, the company plans to start two studies for SMARCB1-deficient tumors: a Phase II trial in adults and a Phase I trial in pediatric patients.

Eisai is eligible for up to $20 million in clinical milestones and up to $50 million in regulatory milestones, plus mid-teens royalties on ex-Japan sales. Epizyme is eligible for mid-teens royalties on sales in Japan. Eisai will fund all Japan-specific development costs, and Epizyme will fund development costs elsewhere. Eisai will have a limited right of first negotiation for Asian rights if Epizyme decides to license those rights to a third party. Epizyme said it has received $39 million from Eisai under the original 2011 deal (see BioCentury, March 14, 2011).

Epizyme disclosed.

Janssen received a not approvable letter from FDA for an NDA for Zarnestra commercialization milestones, plus tiered royalties. In 2005, J&J into Kura shares in conjunction with Kura’s $60 million private placement. Janssen has right of first negotiation to license the farnesyl transferase inhibitor back from Kura within 60 days of completion of the Phase II to treat HRAS mutant tumors. Janssen has right of first negotiation to license the farnesyl transferase inhibitor back from Kura within 60 days of completion of the Phase II to treat HRAS mutant tumors.

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

Cardinal Health Inc., (NYSE:CAH), Dublin, Ohio

Business: Cardiovascular

Johnson & Johnson’s Ethicon Inc. subsidiary will sell its Cordis cardiology and endovascular devices company to Cardinal Health for $1.9 billion in cash. Cardinal expects the purchase to be accretive in 2017. The transaction is slated to close by year end. Cordis had 2014 sales of about $780 million.

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

Kura Oncology Inc., La Jolla, Calif.

Business: Cancer

Johnson & Johnson’s Janssen Pharmaceutica N.V. unit granted Kura exclusive, worldwide rights to develop and commercialize tipifarnib to treat cancer. Kura plans to start a Phase II trial of tipifarnib to treat solid tumors expressing v-Ha-ras Harvey rat sarcoma viral oncogene homolog (HRAS) mutations in 2Q15 and a Phase II trial to treat relapsed or refractory peripheral T cell lymphoma in 3Q15. Janssen has right of first negotiation to license the farnesyl transferase inhibitor back from Kura within 60 days of completion of the Phase II to treat HRAS mutant tumors.

Janssen received a $1 million promissory note that converted into Kura shares in conjunction with Kura’s $60 million private placement. Janssen is eligible for undisclosed development and commercialization milestones, plus tiered royalties. In 2005, J&J received a not approvable letter from FDA for an NDA for Zarnestra
tipifarnib to treat elderly patients with newly diagnosed acute myelogenous leukemia (AML) (see BioCentury, July 4, 2005).

**NanoCarrier Co. Ltd.** (Tokyo:4571), Kashiwa, Japan
**Chugai Pharmaceutical Co. Ltd.** (Tokyo:4519), Tokyo, Japan

Business: Cancer, Drug delivery

NanoCarrier and Chugai partnered to develop a short interfering RNA cancer drug using Chugai’s antibodies and siRNA in combination with NanoCarrier’s NanoFect nucleic acid delivery technology. Chugai will have a priority right to acquire exclusive use of NanoCarrier’s patents or deliverables. Chugai will make an undisclosed payment to NanoCarrier for the option. NanoCarrier will issue 389,400 third-party shares to Chugai valued at ¥500 million ($4.2 million).

**OnCore Biopharma Inc.**, Doylestown, Pa.
**Tekmira Pharmaceuticals Corp.** (NASDAQ:TKMR), Burnaby, B.C.

Business: Infectious

Tekmira completed its merger with OnCore. The merged company will operate as Tekmira and will continue to trade under the TKMR ticker until a new corporate identity is launched and its ticker symbol is changed (see BioCentury, Jan. 19).

**Onxeo S.A.** (Euronext:ONXEO;CSE:ONXEO), Paris, France
**Dara BioSciences Inc.** (NASDAQ:DARA), Raleigh, N.C.

Business: Infectious

Onxeo granted Dara exclusive rights in the U.S. to commercialize Oravig micronazole, which is approved to treat oropharyngeal candidiasis. Additionally, Dara has the right to pursue regulatory approval in Canada, which if granted would give Dara exclusive rights to commercialize the product there. Dara will book revenues and pay Onxeo undisclosed sales milestones. Dara will conduct a pediatric study as part of a postmarketing commitment, which may provide for an expanded indication.

Onxeo considered Oravig a non-strategic drug. Dara also partnered with Mission Pharmacal Co. (San Antonio, Texas) to co-promote the mucoadhesive buccal tablet of micronazole in the primary care market, while Dara will promote the product in the oncology market. Dara, which plans to launch the product in 4Q15, declined to disclose terms of either deal.

**Orca Pharmaceuticals Ltd.**, Oxford, U.K.
**AstraZeneca plc** (LSE:AZN;NYSE:AZN), London, U.K.

Business: Autoimmune

AstraZeneca will gain access to Orca’s inhibitors of RAR-related orphan receptor C (RORC; RORgamma). According to the parties, the compounds can be developed to treat autoimmune diseases. AZ has the option to purchase Orca compounds after the three-year deal. The companies did not respond to requests for details.

**Pharmaxis Ltd.** (ASX:PX;Pink:PXSLY), Frenchs Forest, Australia
**Boehringer Ingelheim GmbH**, Ingelheim, Germany

Business: Hepatic, Inflammation

Boehringer Ingelheim received an exclusive option to license worldwide rights to Pharmaxis’ PXS4728A and related molecules. Pharmaxis will receive €1.3 million ($1.4 million) for the option, which expires on May 15. PXS4728A, an oral vascular adhesion protein-1 (VAP-1; SSAO) inhibitor, is in Phase I testing to treat inflammatory disease. According to Pharmaxis, Boehringer’s primary interest in the compound is directed at non-alcoholic steatohepatitis (NASH).

If the option is exercised, Pharmaxis will receive €27.5 million ($29.9 million) and will be eligible for undisclosed milestone payments triggered by Phase II and III trial starts; submission of marketing applications; regulatory approvals in major markets; and development and approval of additional indications. Pharmaxis will also be eligible for undisclosed sales milestones and earn-out payments. The companies could not be reached for details in time for publication.

**R-Tech Ueno Ltd.** (JASDAQ:4573), Tokyo, Japan
**Sucampo Pharmaceuticals Inc.** (NASDAQ:SCMP), Bethesda, Md.

Business: Ophthalmic

Sucampo returned all rights to unoprostone isopropyl (UF-021) to R-Tech after the product missed the primary endpoint in a Japanese Phase III trial to treat retinitis pigmentosa (RP). Last year, Sucampo ceased marketing Rescula unoprostone isopropyl, which is approved in the U.S. and over 45 countries to treat open-angle glaucoma or ocular hypertension. Sucampo had exclusive rights from R-Tech to develop and commercialize Rescula worldwide outside of Japan, Korea, Taiwan and China under an amended 2009 deal (see BioCentury, March 2).

**Salix Pharmaceuticals Ltd.** (NASDAQ:SLXP), Raleigh, N.C.
**Endo International plc** (NASDAQ:ENDP;TSX:ENL), Dublin, Ireland

Business: Gastrointestinal

Endo submitted a proposal to acquire Salix for $175 per share in cash and stock, or about $11.2 billion. The price, an 11% premium to Salix’s close of $157.65 on March 10, the day before the deal was announced, comprises 1.46 shares of Endo stock and $45 in cash per Salix share.

Last month, **Valent Pharmaceuticals International Inc.** (TSX:VRX; NYSE:VRX, Laval, Quebec) offered to acquire Salix for $158 per share in cash, or $10.2 billion. At the time, Valent said the deal had a total enterprise value of $14.5 billion. Endo also said the offer is an 11% premium over the existing offer from Valent. Although
both the board of Salix and Valeant approved the deal, Endo said it believes its proposal constitutes a “superior proposal” under the terms of the agreement between Salix and Valeant. If accepted, Endo said it expects the deal to close next quarter. Valeant said in a statement that it is “firmly committed” to its offer and expects to close the transaction on April 1. If Salix backs out of its deal with Valeant, Salix would owe Valeant a breakup fee of $356.4 million plus out-of-pocket expenses of up to $50 million. Salix said it is reviewing the offer and advised its stockholders to take no action (see BioCentury, March 2).

Salix markets gastrointestinal drugs, including Xifaxan rifaximin. The company markets the non-absorbed, broad-spectrum antibiotic in the U.S. and Canada to reduce the risk of overt hepatic encephalopathy recurrence in patients with advanced liver disease and to treat travelers’ diarrhea caused by noninvasive strains of Escherichia coli. An sNDA for Xifaxan to treat irritable bowel syndrome with diarrhea (IBS-D) is under FDA review; the PDUFA date is in May. Salix had $1.1 billion in sales for the 2014. Endo had $2.9 billion in sales for 2014.

Salk Institute for Biological Studies, La Jolla, Calif.
Business: Pharmaceuticals
The institute granted MitoBridge exclusive, worldwide rights to develop and commercialize technology and compounds related to PPAR delta. The Salk Institute is eligible for undisclosed milestones. Both parties declined to disclose additional financial terms.

Theratechnologies Inc. (TSX:TH), Montreal, Quebec
AOP Orphan Pharmaceuticals AG, Vienna, Austria
Business: Endocrine/Metabolic
Theratechnologies granted AOP Orphan exclusive rights to develop and commercialize Egrifta tesamorelin in select countries within Europe. AOP Orphan will distribute Egrifta in the countries through Named Patient Sales Programs and will be responsible for regulatory activities. The analog of growth hormone-releasing factor is approved in the U.S. to treat excess abdominal fat in HIV patients with lipodystrophy. Theratechnologies will receive €150,000 ($162,825) up front and is eligible for up to €3 million ($3.3 million) in milestones, plus royalties.

Zogenix Inc. (NASDAQ:ZGNX), San Diego, Calif.
Pernix Therapeutics Holdings Inc. (NASDAQ:PTX), Morristown, N.J.
Business: Neurology
Pernix will acquire the Zohydro ER analgesic franchise from Zogenix. The franchise includes Zohydro ER, an oral controlled-release formulation of hydrocodone; Zohydro ER with BeadTek, an oral controlled-release formulation of hydrocodone that uses an inactive ingredient that deters abuse by forming a viscous gel when crushed and dissolved in solvents; and ZX007, an abuse-deterrent tablet formulation. Pernix will pay Zogenix $100 million up front, including a minimum of $30 million in cash, $20 million in stock and a six-month promissory note for $50 million that accrues interest at LIBOR plus 3%. Zogenix is eligible for a $12.5 million milestone upon approval of ZX007 and up to $271 million in sales milestones. Zogenix launched Zohydro ER in March 2014. FDA approved Zohydro ER with BeadTek in January, and Pernix expects to launch the drug in April. Both are approved to manage pain severe enough...
to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Pernix hopes to submit an sNDA in 2H15 to add abuse-deterrence to the label of Zohydro ER with BeadTek and an NDA in mid-2016 for ZX007. Pernix said ZX007 has patent protection through 2030.

Pernix expects the deal to close in April. It plans to hire Zogenix's Zohydro ER sales force of about 100 representatives.

COMPANY NEWS

SALES & MARKETING

Chugai Pharmaceutical Co. Ltd. (Tokyo:4519), Tokyo, Japan
Business: Cancer
Chugai launched Zelboraf vemurafenib in Japan to treat unresectable melanoma with a BRAF mutation. The mutation is identified using the cobas 4800 BRAF V600 Mutation Test from Roche (SIX:ROG; OTCQX:RHHBY, Basel, Switzerland), which is the majority owner of Chugai. The National Health Insurance (NHI) reimbursement price for a 240 mg tablet is ¥4,935.50 ($40.96). The usual dose is 960 mg twice daily.

Zelboraf is available in more than 80 countries. Roche has exclusive, worldwide rights to the oral small molecule inhibitor of the oncogenic BRAF V600E from Daiichi Sankyo Co. Ltd. (Tokyo:4568, Tokyo, Japan).

Eisai Co. Ltd. (Tokyo:4523), Tokyo, Japan
Business: Cancer
Eisai said the Cancer Drugs Fund (CDF) panel upheld an appeal from the company to reconsider a January decision from NHS England to remove breast cancer drug Halaven eribulin mesylate from the CDF. Eisai said the decision came one day before Halaven was slated to lose CDF coverage. The drug will now remain on the CDF pending reconsideration this month (see BioCentury, Jan. 12).

The fund is intended to give patients access to drugs that would not otherwise be available on the NHS. The synthetic analog of halichondrin B is approved in the EU to treat locally advanced or metastatic breast cancer in patients whose disease has progressed after at least one chemotherapy regimen for advanced disease.

Meridian Bioscience Inc. (NASDAQ:VIVO), Cincinnati, Ohio
Business: Diagnostic
Meridian launched the TRU Strep Pneumo assay in Europe, the Middle East and Africa to detect Streptococcus pneumoniae in urine and cerebrospinal fluid. The in vitro lateral-flow immunoassay has CE Mark approval.

Otsuka Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
Business: Gastrointestinal
Takeda and Otsuka launched Takecab vonoprazan fumarate in Japan to treat acid-related diseases. The National Health Insurance (NHI) reimbursement price for a 10 mg tablet is ¥160.1 ($1.33) and ¥240.2 ($1.99) for a 20 mg tablet. Dosage and length of treatment depends on the indication. Takeda owns Takecab and partnered with Otsuka to co-promote the small molecule potassium-competitive acid blocker in Japan last March. Otsuka will receive a co-promotion fee based on sales (see BioCentury, March 31, 2014).

COMPANY NEWS

OTHER NEWS

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Business: Cancer
Amgen will close the headquarters of its cancer-focused Onyx Pharmaceuticals Inc. subsidiary in South San Francisco, California, and lay off about 300 of the subsidiary’s 750 employees by year end, according to an internal memo. Onyx and Amgen cancer functions will be combined and report into the existing Amgen organization. Some Onyx R&D roles will move to Amgen’s research facility in South San Francisco. Amgen said it had no imminent plans to terminate specific projects under development at Onyx. Amgen acquired Onyx in 2013 (see BioCentury, Oct. 7, 2013).

BioMarin Pharmaceutical Inc. (NASDAQ:BMRN), Novato, Calif.
Business: Endocrine/Metabolic
The U.S. Patent and Trademark Office’s Patent Trial and Appeal Board (PTAB) invalidated three patents covering methods for treating Pompe’s disease on the grounds of obviousness. BioMarin filed petitions requesting inter partes review of the patents. The patents — U.S. Patent Nos. 7,655,226 and 7,351,410 from Sanofi’s Genzyme Corp. unit and U.S. Patent No. 7,056,712 B2 from Duke University — covered a method of using a “therapeutically effective” amount of human acid alpha glucosidase (GAA) to treat Pompe’s disease. Genzyme’s ’226 and ’410 patents were set to expire in 2019 and 2020, respectively. Duke’s ’712 patent was set to expire in 2023. Genzyme markets Myozyme/Lumizyme alglucosidase alpha for Pompe’s disease, which had sales of €542 million ($660.2 million) in 2014. Genzyme plans to appeal to the U.S. Federal Circuit. Genzyme is also developing Neo-GAA, a second-generation recombinant human GAA enzyme, which is in Phase I testing for the indication. BioMarin is developing BMN 701, a fusion of insulin-like growth factor-2 (IGF-2) and GAA that uses Glycosylation Independent Lysosomal Targeting (GILT) technology. BMN 701 is Phase III
trials to treat late-onset Pompe’s disease and has Orphan Drug designation in the U.S.

BioMarin noted that the PTAB decision “does not have a material impact on us as we believe that BMN 701 did not infringe those patents and would not infringe those patents if commercialized.”

Canon Inc. (Tokyo:7751; NYSE:CAJ), Tokyo, Japan
Business: Other
Canon established Canon BioMedical Inc., a wholly owned subsidiary to serve as a headquarters for its biomedical business. The subsidiary will develop and market its life science and molecular diagnostics platform. Canon said Canon BioMedical “will look for long-term future growth opportunities in previously untapped markets for Canon such as life science, healthcare, and medical analysis through the use of existing and emerging Canon technology, as well as strategic partnerships.”

Celltrion Inc. (KOSDAQ:068270), Incheon, South Korea
Hospira Inc. (NYSE:HSP), Lake Forest, Ill.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
New York University, New York, N.Y.
Business: Autoimmune, Biosimilars

Johnon & Johnson’s Janssen Biotech Inc. unit and New York University filed a suit in the U.S. District Court for the District of Massachusetts seeking to delay or block the U.S. launch of CT-P13, a biosimilar of J&J’s autoimmune drug Remicade infliximab. The suit alleges Celltrion and Hospira tried to bypass the patent dispute resolution procedures of the Biologics Price Competition and Innovation Act (BPCIA) by filing two declaratory judgment suits in 2014 seeking protection from patent infringement allegations. The court dismissed one suit, and Celltrion withdrew the other. Janssen and NYU also argue that the defendants refused to provide manufacturing information as required by BPCIA.

Additionally, Janssen and NYU allege that CT-P13 infringes six patents covering Remicade. Two of the patents are co-owned by the plaintiffs, including U.S. Patent No. 6,284,471, which the U.S. Patent and Trademark Office rejected in February, and U.S. Patent No. 7,223,396, which expires June 29, 2016. Janssen owns the other patents, U.S. Patent Nos. 5,807,715; 6,773,600; 7,598,083; and 6,900,056. The '396 patent covers methods of producing antibodies and expires Sept. 15, 2015, while the '600 patent covers methods of purification and expires June 4, 2023. The '083 and '056 patents cover cell growth media and expire Feb. 7, 2027, and Oct. 5, 2022, respectively. On Feb. 12, J&J said it had 60 days to respond to the '471 rejection.

The plaintiffs are seeking damages, an order compelling Celltrion and Hospira to comply with the BPCIA and an enjoinder preventing the defendants from marketing any compound that violates the relevant patents. Hospira declined to comment, and Celltrion did not respond to inquiries. J&J and NYU are also seeking an injunction preventing Celltrion or Hospira from marketing CT-P13 in the U.S. until 180 days after they provide “proper” notice of commercial marketing once CT-P13 is approved.

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

Merck discontinued discovery and non-clinical operations at its Cubist Pharmaceuticals Inc. subsidiary in Lexington, Massachusetts. The move will cut about 120 jobs at the site. Merck said that select Cubist discovery projects will be transferred to Merck sites, but declined to provide details. The cuts will not affect development of later stage products at the site. Merck completed its acquisition of Cubist in January (see BioCentury, Dec. 15, 2014 & Feb. 2, 2015).

Mitsubishi Tanabe Pharma Corp. (Tokyo:4508), Osaka, Japan
U.S. Department of Health and Human Services, Washington, D.C.
Business: Infectious

HHS’s Biomedical Advanced Research and Development Authority (BARDA) awarded Mitsubishi’s Medicago Inc. subsidiary a contract to manufacture three mAbs against the Ebola virus for a study in non-human primates. Two of the mAbs were discovered by Public Health Agency of Canada. Medicago said it intends to compare the performance of its mAbs to Zmapp from Mapp Biopharmaceutical Inc. (San Diego, Calif.). Medicago’s platform uses Nicotiana plants as a production system.

Mapp also uses the Nicotiana plant to produce Zmapp, which is a combination of three mAbs targeting Ebola glycoproteins GP1 and GP2, but it has struggled to keep up with demand for Zmapp during the Ebola outbreak. Zmapp has not been tested for efficacy and safety in humans, but has been shown to reverse 100% of advanced Ebola cases in primates (see BioCentury, Aug. 11, 2014; Sept. 1, 2014 & Sept. 8, 2014).
ABBVie Inc. (NYSE: ABBV), Chicago, Ill.
Eisai Co. Ltd. (Tokyo: 4523), Tokyo, Japan
Product: Humira adalimumab
Business: Autoimmune
The U.K.’s NICE issued a final guidance recommending 3 mAbs against tumor necrosis factor (TNF) alpha to treat moderately to severely active ulcerative colitis (UC): Remicade infliximab from Johnson & Johnson (NYSE: JNJ, New Brunswick, N.J.) and Merck & Co. Inc. (NYSE: MRK, Whitehouse Station, N.J.); Humira adalimumab from AbbVie and Eisai; and Simponi golimumab from J&J and Merck. Specifically, the drugs are recommended in adults whose disease has responded inadequately to conventional therapy, including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate or have medical contraindications for such therapies — their approved indications.
Remicade is also approved for the indication in patients ages 6-17 years, for which NICE also recommended the drug. The drugs should be given until treatment failure or until 12 months after starting treatment — whichever is shorter. The final guidance for Simponi is contingent on Merck providing the 100 mg dose at the same cost as the 50 mg dose under a patient access scheme.
The final guidance is in line with the final appraisal determination (FAD) (see BioCentury, Sept. 29, 2014 & Dec. 22, 2014). Merck has rights to market Simponi in Europe, Russia and Turkey.

Acadia Pharmaceuticals Inc. (NASDAQ: ACAD), San Diego, Calif.
Product: Nuplazid pimavanserin (formerly ACP-103)
Business: Neurology
Acadia said it will delay submission of an NDA to FDA to 2H15 from 1Q15 for Nuplazid pimavanserin to treat Parkinson’s disease psychosis (PDP). The company said it needs additional time to prepare its commercial manufacturing systems. The small molecule serotonin (5-HT2A) receptor inverse agonist has breakthrough therapy designation in the U.S. for PDP.

AcelRx Pharmaceuticals Inc. (NASDAQ: ACRX), Redwood City, Calif.
Product: Zalviso sufentanil (ARX-01) (formerly Sufentanil NanoTab PCA System)
Business: Neurology
AcelRx delayed its resubmission of an NDA for Zalviso sufentanil sublingual tablet system to treat moderate to severe acute pain after FDA requested an additional clinical trial to “assess the risk of inadvertent dispensing and overall risk of dispensing failures.” AcelRx had hoped to resubmit the NDA this quarter.

Apotex Inc., Toronto, Ontario
Stada Arzneimittel AG (Xetra: SAZ), Bad Vilbel, Germany
Product: Grastofil filgrastim
Business: Hematology
FDA accepted for review a BLA from Apotex for Grastofil, a biosimilar of neutropenia drug Neupogen filgrastim from Amgen Inc. (NASDAQ: AMGN, Thousand Oaks, Calif.). Grastofil is already marketed in Europe by Stada under a 2013 deal (see BioCentury, Nov. 4, 2013).

In July 2014, AcelRx said it received a complete response letter from FDA for an NDA for Zalviso requesting additional information to “ensure proper use” of the pre-programmed, handheld device that delivers a sublingual formulation of sufentanil, a synthetic opioid analgesic. In the letter, FDA did not request additional clinical trials (see BioCentury, Aug. 4, 2014).
AcelRx has since performed bench testing and 2 human factors studies to address the agency’s concerns. The company will provide an updated resubmission timeline after it meets with FDA to discuss the design and objectives of the new trial.

Alexion Pharmaceuticals Inc. (NASDAQ: ALXN), Cheshire, Conn.
Product: Soliris eculizumab
Business: Hematology
EMA’s CHMP recommended approval of an expanded label for Orphan drug Soliris eculizumab from Alexion to treat paroxysmal nocturnal hemoglobinuria (PNH) to include transfusion-naive or transfusion-experienced patients with high disease activity. The approved label says evidence of Soliris’ clinical benefit is limited to transfusion-experienced PNH patients. Alexion said CHMP also recommended the addition of data to the label on the benefits of long-term treatment and the risks associated with treatment discontinuation in patients with atypical hemolytic uremic syndrome (aHUS) — its other approved indication. The humanized mAb targeting complement 5 (C5) is approved in the U.S. to treat aHUS and PNH.

Anika Therapeutics Inc. (NASDAQ: ANIK), Bedford, Mass.
Product: Cingal
Business: Autoimmune
Anika submitted a PMA in the U.S. for Cingal to treat osteoarthritis (OA) of the knee. Anika also submitted an application for CE Mark approval in the EU at the end of last year. Cingal is a single injection of sodium hyaluronate with triamcinolone hexaonide. The applications included data from a double-blind, placebo-controlled Phase III trial in 368 patients with joint pain caused by OA of the knee, in which the company said Cingal met all primary and secondary endpoints.

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Neupogen, a recombinant methionyl human G-CSF (CSF3), is approved to treat cancer patients receiving myelosuppressive chemotherapy; patients with acute myelogenous leukemia (AML) receiving induction or consolidation chemotherapy; cancer patients receiving bone marrow transplant; patients undergoing peripheral blood progenitor cell collection and therapy; and patients with severe chronic neutropenia.

BioCentury

**Week in Review**

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

**Product**: Crescema isavuconazonium, isavuconazole (BAL8557)
**Business**: Infectious

FDA approved an NDA from Astellas for Crescema isavuconazonium to treat invasive aspergillosis and mucormycosis in adults. The agency approved both IV and oral formulations of the prodrug of isavuconazole, a broad-spectrum water-soluble azole antifungal. Astellas declined to discuss launch plans. The label includes a warning that Crescema shortened the QTc interval in a concentration-related manner and the drug is contraindicated in patients with familial short QT syndrome. The approval triggered a CHF30 million ($30.4 million) milestone payment to Basilea from Astellas.

Crescema has Qualified Infectious Disease Product (QIDP) and Orphan Drug status in the U.S. for both indications. The product is under review in Europe for the indications. Astellas and Basilea are co-developing and commercializing isavuconazonium outside Japan under an amended 2010 deal (see BioCentury, March 1, 2010 & March 3, 2014).

**BioDelivery Sciences International Inc.** (NASDAQ:BDSI), Raleigh, N.C.
**Endo International plc** (NASDAQ:ENDP; TSX:ENL), Dublin, Ireland

**Product**: Belbucabuprenorphine buccal film (BEMA Buprenorphine) (EN3409) (formerly BEMA LA)
**Business**: Neurology

BioDelivery and Endo said FDA accepted for review an NDA for Belbucabuprenorphine buccal film to manage pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. The PDUFA date is in October. The NDA acceptance triggered a $10 million milestone payment to BioDelivery under a 2012 deal granting Endo exclusive, worldwide rights to develop and commercialize the product to treat chronic pain (see BioCentury, Jan. 9, 2012). The partners are developing the buprenorphine formulation with the BEMA transmucosal delivery system under section 505(b)(2) of the Food, Drug and Cosmetic Act, which allows sponsors to reference data on safety and efficacy from the scientific literature or from previously approved products.

**BioGen Idec Inc.** (NASDAQ:BIIB), Cambridge, Mass.

**Product**: Tecfidera dimethyl fumarate (formerly BG-12)
**Business**: Autoimmune

The Drug Controller General of India (DCGI) approved Tecfidera dimethyl fumarate from Biogen Idec to treat relapsing-remitting multiple sclerosis (RRMS). The oral dimethyl fumarate that activates the NF-E2-related factor 2 (Nrf2) pathway is now available in the country. Tecfidera is approved in the U.S., EU, Canada and Australia.

**Samsung Group**, Seoul, South Korea

**Product**: SB2
**Business**: Autoimmune

Samsung Bioepis Co. Ltd. submitted an MAA to EMA for SB2, a biosimilar of autoimmune drug Remicade infliximab from Johnson & Johnson (NYSE:JNJ, New Brunswick, N.J.) and Merck & Co. Inc. (NYSE:MRK, Whitehouse Station, N.J.). Samsung Bioepis is a JV between Biogen Idec and Samsung. Biogen Idec will commercialize the biosimilar in Europe, if approved. Remicade, a chimeric mAb against tumor necrosis factor (TNF) alpha, is indicated in the EU to treat Crohn’s disease (CD), ulcerative colitis (UC), rheumatoid arthritis, ankylosing spondylitis (AS), psoriasis and psoriatic arthritis.

**bioLytical Laboratories Inc.**, Richmond, B.C.

**Product**: Insti HIV/Syphilis Multiplex Test
**Business**: Infectious

bioLytical received CE Mark approval for the Insti HIV/Syphilis Multiplex Test to simultaneously detect syphilis, HIV-1 and HIV-2 antibodies. The *in vitro* test detects antibodies in human whole blood, serum or plasma and delivers results in about 60 seconds.

**Celgene Corp.** (NASDAQ:CELG), Summit, N.J.
**Taiho Pharmaceutical Co. Ltd.**, Tokyo, Japan

**Product**: Abraxane nab-paclitaxel (ABI-007)
**Business**: Cancer

The European Commission approved an expanded label for Abraxane nab-paclitaxel from Celgene to include first-line treatment of non-small cell lung cancer (NSCLC) in combination with carboplatin in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. The albumin stabilized nanoparticle formulation of paclitaxel is approved in the EU for second-line treatment of metastatic breast cancer and first-line treatment of metastatic pancreatic cancer in combination with gemcitabine. Taiho, a subsidiary of Otsuka Holdings Co. Ltd. (Tokyo:4578, Tokyo, Japan), has Japanese rights to the product from Celgene.
WEEK IN REVIEW

Collegium Pharmaceutical Inc., Canton, Mass.
Product: Xtampza ER oxycodone extended-release
Business: Neurology
FDA accepted for review an NDA for oral Xtampza ER oxycodone extended-release from Collegium to treat chronic pain. Collegium submitted the NDA in December; the PDUFA date was not disclosed. The abuse-deterrent analgesic uses the company’s DETERx tamper resistance technology. Collegium said the abuse-deterrent properties of Xtampza ER make it more difficult to abuse or misuse via oral administration after chewing or crushing; snorting; smoking; or injection.

Corgenix Medical Corp. (OTCBB: CONX), Broomfield, Colo.
Product: ReEBOV Antigen Rapid Test
Business: Diagnostic
The World Health Organization (WHO) approved the ReEBOV Antigen Rapid Test from Corgenix to detect Ebola virus in fingerstick whole blood, plasma and serum specimens. The agency approved the test under its Emergency Assessment and Use procedure. The rapid chromatographic immunoassay qualitatively detects the VP40 antigen from Ebola viruses, with results in about 15-25 minutes. WHO said that although ReEBOV is less accurate than the current test it uses, it is easy to perform, does not require electricity and can be used at lower level facilities or in mobile units.

Eisai Co. Ltd. (Tokyo: 4523), Tokyo, Japan
Novartis AG (NYSE: NVS; SIX: NOVN), Basel, Switzerland
Product: Banzel rufinamide (Inovelon) (SYN-111)
Business: Neurology
FDA approved an sNDA from Eisai for Banzel rufinamide as an adjunct treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ages 1-4. Eisai markets the triazole derivative in the U.S. as Banzel and in the EU as Inovelon as adjunctive treatment of seizures associated with LGS in patients ages ≥4 years.

Eisai has exclusive, worldwide rights from Novartis to rufinamide for indications other than bipolar mood disorder, anxiety disorders and ophthalmologic disorders. Biotie Therapies Corp. (HSE: BTHIV, Turku, Finland) has exclusive, worldwide rights outside of Japan from Novartis to rufinamide to treat anxiety and bipolar mood disorders (see BioCentury, Feb. 7, 2011).

Enanta Pharmaceuticals Inc. (NASDAQ: ENTA), Watertown, Mass.
AbbVie Inc. (NYSE: ABBV), Chicago, Ill.
Product: Viekirax (paritaprevir (ABT-450) plus ritonavir/ombitasvir (ABT-267))
Business: Infectious
AbbVie submitted an NDA to Japan’s Ministry of Health, Labor and Welfare (MHLW) for an all-oral, interferon-free treatment of hepatitis C virus (HCV) genotype 1 infection. The company said the NDA is supported by data from the Phase III GIFT-1 trial (see BioCentury, Feb. 9). The product is a combination of paritaprevir, an HCV NS3/4A protease inhibitor, plus booster Norvir ritonavir and ombitasvir, an HCV NS5A protein inhibitor. AbbVie markets Norvir, an HIV protease inhibitor. Paritaprevir is partnered with Enanta.

Gilead Sciences Inc. (NASDAQ: GILD), Foster City, Calif.
Product: Sovaldi sofosbuvir (GS-7977) (formerly PSI-7977)
Business: Infectious
The U.K.’s NICE issued final guidance recommending Gilead’s Sovaldi sofosbuvir to treat chronic HCV infection in combination with ribavirin, with or without peginterferon alfa (IFN). Specifically, Sovaldi is recommended in combination with IFN and ribavirin in patients with genotype 1 infection; in treatment-experienced patients with genotype 3 infection; in treatment-naïve patients with genotype 3 infection and cirrhosis; and in patients with genotype 4, 5 or 6 infection and cirrhosis. It is recommended in combination with ribavirin in treatment-experienced patients with genotype 2 infection; in treatment-naïve patients with genotype 2 infection who are intolerant to or ineligible for IFN; in patients with genotype 3 infection and cirrhosis who are intolerant to or ineligible for IFN. Sovaldi plus ribavirin is not recommended in patients with genotype 1, 4, 5 or 6 infection. Sovaldi plus ribavirin and IFN is not approved in patients with genotype 2 infection. Gilead markets Sovaldi, a nucleotide analog HCV NS5B polymerase inhibitor, in the U.S., EU and Canada to treat HCV infection.

Institut Biochimique S.A., Lugano, Switzerland
Product: Beteflam Patch (Betesil Patch)
Business: Dermatology
Health Canada accepted for review an NDS for Beteflam Patch from Cipher Pharmaceuticals Inc. (TSX: DND; NASDAQ: CPHR, Mississauga, Ontario) to treat inflammatory skin conditions, including chronic plaque psoriasis. The company said it expects a decision at the end of November. The acceptance triggered a C$150,000 ($119,910) payment to Institut Biochimique from Cipher under a 2012 deal granting Cipher marketing rights to the product in Canada (see BioCentury, Aug. 13, 2012). Beteflam Patch is a self-adhesive medicated plaster containing 0.1% betamethasone valerate.

Johnson & Johnson (NYSE: JNJ), New Brunswick, N.J.
Merck & Co. Inc. (NYSE: MRK), Whitehouse Station, N.J.
Product: Remicade infliximab (formerly TA-650)
Business: Autoimmune
The U.K.’s NICE issued a final guidance recommending 3 mAbs against tumor necrosis factor (TNF) alpha to treat moderately to severely active ulcerative colitis (UC). Remicade infliximab from...
Johnson & Johnson and Merck; Humira adalimumab from AbbVie Inc. (NYSE:ABBV, Chicago, Ill.) and Eisai Co. Ltd. (Tokyo:4523, Tokyo, Japan); and Simponi golimumab from J&J and Merck. Specifically, the drugs are recommended in adults whose disease has responded inadequately to conventional therapy, including corticosteroids and mercapto purine or azathioprine, or who cannot tolerate or have medical contraindications for such therapies — their approved indications.

Remicade is also approved for the indication in patients ages 6-17 years, for which NICE also recommended the drug. The drugs should be given until treatment failure or until 12 months after starting treatment — whichever is shorter. The final guidance for Simponi is contingent on Merck providing the 100 mg dose at the same cost as the 50 mg dose under a patient access scheme.

The final guidance is in line with the final appraisal determination (FAD) (see BioCentury, Sept. 29, 2014 & Dec. 22, 2014). Merck has rights to market Simponi in Europe, Russia and Turkey.

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Business: Autoimmune
The U.K.’s NICE issued a final guidance recommending 3 mAbs against tumor necrosis factor (TNF) alpha to treat moderately to severely active ulcerative colitis (UC): Remicade infliximab from Johnson & Johnson and Merck & Co. Inc. (NYSE:MRK, Whitehouse Station, N.J.); Humira adalimumab from AbbVie Inc. (NYSE:ABBV, Chicago, Ill.) and Eisai Co. Ltd. (Tokyo:4523, Tokyo, Japan); and Simponi golimumab from J&J and Merck. Specifically, the drugs are recommended in adults whose disease has responded inadequately to conventional therapy; including corticosteroids and mercapto purine or azathioprine, or who cannot tolerate or have medical contraindications for such therapies — their approved indications.

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Kythera Biopharmaceuticals Inc. (NASDAQ:KYTH), Calabasas, Calif.
Product: Deoxycholic acid (ATX-101)
Business: Other
FDA’s Dermatologic and Ophthalmic Drugs Advisory Committee voted 17-0 to recommend approval of ATX-101 to reduce submental (under chin) fat. The PDUFA date is May 13. If approved, Kythera plans to launch the synthetic sodium deoxycholate next half. The company said ATX-101 would be the first approved non-surgical method of reducing submental fat. Kythera has submitted regulatory applications for the product in Canada, Switzerland and Australia.

In briefing documents released ahead of the meeting, FDA reviewers said ATX-101 met the primary endpoints of achieving ≥2-grade improvement from baseline to 12 weeks vs. placebo on clinician- and patient-reported submental fat rating scales (p<0.001 for both). The reviewers found no major safety issues.

Ligand Pharmaceuticals Inc. (NASDAQ:LGND), La Jolla, Calif.
Spectrum Pharmaceuticals Inc. (NASDAQ:SPPI), Henderson, Nev.
Product: IV Captisol-enabled Melphalan
Business: Transplant
FDA accepted for review an NDA from Spectrum for IV Captisol-enabled Melphalan as a high-dose conditioning treatment in multiple myeloma (MM) patients undergoing autologous stem cell transplantation (ASCT) and for palliative treatment of MM patients for whom oral therapy is not appropriate. The PDUFA date is Oct. 23. The propylene glycol-free formulation of melphalan is delivered via Captisol sulfobutylether beta-cyclodextrin technology.

The NDA 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 the scientific literature or from previously approved products. Spectrum has exclusive, worldwide rights from Ligand to develop and commercialize the product under a 2013 deal (see BioCentury, March 18, 2013).

Medivir AB (SSE:MVIR B), Huddinge, Sweden
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Product: Olysio simeprevir (Soviad, Galexos) (TMC435) (formerly TMC435350)
Business: Infectious
The U.K.’s NICE issued final guidance recommending Olysio simeprevir from Medivir and Johnson & Johnson to treat chronic HCV genotypes 1 and 4 infection in combination with peginterferon alfa and ribavirin. The guidance is in line with the final appraisal determination (FAD) (see BioCentury, Feb. 9).

The HCV NS3/4A protease inhibitor is approved in the EU to treat HCV genotypes 1 and 4 infection in combination with peginterferon, ribavirin and/or Sovaldi sofosbuvir from Gilead Sciences Inc. (NASDAQ:GILD, Foster City, Calif). Recommendations for Olysio in combination with Sovaldi will be developed in a separate guidance. Janssen has ex-Nordic rights to develop and commercialize Olysio from Medivir.

Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Product: Keytruda pembrolizumab (MK-3475) (formerly lambrolizumab)
Business: Cancer
Merck said melanoma therapy pembrolizumab will be the first product offered under the U.K.’s Early Access to Medicines Scheme (EAMS). Merck will provide pembrolizumab for free under EAMS to advanced melanoma patients who have exhausted approved treatment options. The U.K.’s Medicines and Healthcare products Regulatory Agency (MHRA) launched EAMS last April to provide patients who have life threatening conditions with access to candidates that are not yet approved. Merck declined to disclose when it expects a decision from EMA on its MAA for pembrolizumab to treat advanced melanoma, which was accepted for review last June (see BioCentury, July 14, 2014).

Pembrolizumab received a promising innovative medicine (PIM) designation last October, which is given to products that treat conditions that have no treatment options or have unsatisfactory treatment options based on quality, safety and efficacy data from Phase II or III testing. MHRA based its decision on data from the Phase Ib KEYNOTE-001 trial, in which 24% of patients who received a dose of 2 mg/kg every 3 weeks had tumor shrinkage, 47% had halted disease progression and 60% survived for at least 1 year (see BioCentury, June 9, 2014).

Merck said some patients in the U.K. who have already been treated with pembrolizumab under the company’s global expanded access program will transition to EAMS. Merck said 3,500 patients in more than 40 countries have received Keytruda via the expanded access program.

The humanized IgG4 mAb against programmed cell death 1 (PDCD1; PD-1; CD279) is marketed in the U.S. as Keytruda to treat renal cell carcinoma (RCC) and lung cancer. Merck said Keytruda is also under review in the U.S. this summer and will disclose pricing at that time. The chimeric mAb targeting GD2 is also under review in the EU.

Unituxin has a boxed warning that the product irritates nerve cells causing severe pain that requires treatment with IV narcotics and can also cause nerve damage and life-threatening infusion reactions, including upper airway swelling, difficulty breathing and low blood pressure, during or shortly following completion of the infusion. Unituxin may also cause other serious side effects, including infections, eye problems, electrolyte abnormalities and bone marrow suppression. FDA said United Therapeutics has agreed to postmarketing requirements and commitments, but the company declined to disclose details.

With Unituxin’s approval, United Therapeutics also became the second company to receive a voucher under FDA’s Rare Pediatric Disease Priority Review voucher program, which was created by PDUFA V to encourage the development of new drugs and biologics to prevent and treat rare pediatric diseases. The transferrable voucher entitles the holder to obtain Priority Review of any subsequent NDA or BLA that otherwise would receive a standard review.

**CLINICAL RESULTS**

**Acceleron Pharma Inc.** (NASDAQ:XLRN), Cambridge, Mass.
Product: Dalantercept (ACE-041)
Business: Cancer

Molecular target: Activin receptor-like kinase 1 (ACVRL1) (ALK1) (HHT2)
Description: Angiogenesis inhibitor that binds to and prevents members of the transforming growth factor (TGF) beta superfamily from signaling through activin receptor-like kinase 1 (ACVRL1; ALK1; HHT2)
Indication: Treat renal cell carcinoma (RCC)
Week in Review

Molecular target: Serotonin (5-HT2B) receptor
Business: Neurology
Product: Metadoxine ER (MDX) (MG01CI)
Alcobra Ltd.

reported data from the trial (see BioCentury, Nov. 11, 2013). Data were published in
enrolled 24 patients to receive twice-daily 5, 15, 22.5 or 30 mg AKB-9778 of >100 µm in 5 patients and of 50-100 µm in 2 patients. The trial led to reductions in central subfield thickness (CST) in the study eye improving by >15 letters. Additionally, AKB-9778 at doses of ≥15 mg to week 4, with 1 patient improving by 10-15 letters and 2 patients 28 days improved BCV A by ≥5 letters in 13 patients from baseline that twice-daily subcutaneous AKB-9778 at doses of ≥15 mg for
Ib/IIa TIME-1 trial in 18 evaluable patients with DME showed
Acceleron previously reported data from 20 evaluable patients (see BioCentury, May 26, 2014). Part 2 of the trial is enrolling 130 patients and is comparing the recommended Phase II dose of 0.9 mg/kg dalantercept plus Inlyta vs. Inlyta alone in patients who progressed following treatment with 1 VEGF receptor TKI.

Aerpio Therapeutics Inc., Cincinnati, Ohio
Product: AKB-9778
Business: Ophthalmic
Molecular target: Protein tyrosine phosphatase receptor type D (PTPRD) (HPTP) beta
Description: Tyrosine kinase receptor 2 (Tie2) activator
Indication: Treat diabetic macular edema (DME)
Endpoint: Safety; pharmacokinetics, optical coherence tomography (OCT)-measured retinal thickness and best corrected visual acuity (BCVA)
Status: Additional Phase Ib/IIa data
Milestone: Phase II data (2Q15)

Additional data from the open-label, dose-escalation, U.S. Phase Ib/II TIME-1 trial in 18 evaluable patients with DME showed that twice-daily subcutaneous AKB-9778 at doses of ≥15 mg for 28 days improved BCVA by ≥5 letters in 13 patients from baseline to week 4, with 1 patient improving by 10-15 letters and 2 patients improving by >15 letters. Additionally, AKB-9778 at doses of ≥15 mg led to reductions in central subfield thickness (CST) in the study eye of >100 µm in 5 patients and of 50-100 µm in 2 patients. The trial enrolled 24 patients to receive twice-daily 5, 15, 22.5 or 30 mg AKB-9778. Data were published in Ophthalmology. Aerpio previously reported data from the trial (see BioCentury, Nov. 11, 2013).

Alcobra Ltd. (NASDAQ:ADHD), Tel Aviv, Israel
Product: Metadoxine ER (MDX) (MG01CI)
Business: Neurology
Molecular target: Serotonin (5-HT2B) receptor

Description: Extended-release formulation of metadoxine, a selective antagonist of the serotonin (5-HT2B) receptor
Indication: Treat adolescent ADHD
Endpoint: Safety; change in Test of Variables of Attention (TOVA) 8 Attention Performance Index (API), TOVA response rates, Wechsler Intelligence Scale for Children (WISC-IV) subtests and working memory and processing speed and pharmacokinetics
Status: Phase II data
Milestone: NA

A double-blind, placebo-controlled, Israeli Phase II trial in 83 patients ages 13-17 with predominantly inattentive ADHD showed that a single dose of 14-22 mg/kg oral metadoxine ER met the primary safety endpoint. Specifically, metadoxine ER was well tolerated with no safety concerns identified and no discontinuations due to adverse events. The most common adverse events reported were headache, nausea and fatigue. Alcobra also said that metadoxine ER led to no significant improvements on secondary cognitive endpoints, but did produce an “efficacy signal” compared to placebo on the TOVA assessments for response time and errors of omission. Metadoxine ER is also in Phase III testing to treat adult ADHD.

Annias Immunotherapeutics Inc., Chapel Hill, N.C.
Product: PEP-CMV
Business: Cancer
Molecular target: Human cytomegalovirus (CMV) phosphoprotein 65
Description: Autologous dendritic cells pulsed with human cytomegalovirus (CMV) phosphoprotein 65 RNA
Indication: Treat glioblastoma multiforme (GBM)
Endpoint: Safety and feasibility; humoral and cellular immune responses, time to progression and evidence of antigen-escape outgrowth in recurrent or progressive tumors
Status: Phase I/II data
Milestone: Start Phase II (2015)

Researchers at Duke University (Durham, N.C.) reported data from a U.S. Phase I/II trial in 12 patients with newly diagnosed GBM showing that preconditioning the vaccine site with a tetanus/diphtheria toxoid antigen prior to vaccination with PEP-CMV significantly improved progression-free survival (PFS) and overall survival (OS) compared to preconditioning with mature dendritic cells prior to vaccination with PEP-CMV (p=0.013 for both). Additionally, 3 of 6 patients who were preconditioned with a tetanus/diphtheria toxoid antigen prior to vaccination with PEP-CMV survived for >36.6 months. Data were published in Nature. Annias has exclusive, worldwide rights from Duke to IP relating to both targeting CMV in cancer and to the preconditioning technology.

CTI BioPharma Corp. (NASDAQ:CTIC; Milan:CTIC), Seattle, Wash.
Baxter International Inc. (NYSE:BAX), Deerfield, Ill.
Product: Pacritinib (SB1518, ONX 0803)
Business: Hematology

Researchers at Duke University (Durham, N.C.) reported data from a U.S. Phase I/II trial in 12 patients with newly diagnosed GBM showing that preconditioning the vaccine site with a tetanus/diphtheria toxoid antigen prior to vaccination with PEP-CMV significantly improved progression-free survival (PFS) and overall survival (OS) compared to preconditioning with mature dendritic cells prior to vaccination with PEP-CMV (p=0.013 for both). Additionally, 3 of 6 patients who were preconditioned with a tetanus/diphtheria toxoid antigen prior to vaccination with PEP-CMV survived for >36.6 months. Data were published in Nature. Annias has exclusive, worldwide rights from Duke to IP relating to both targeting CMV in cancer and to the preconditioning technology.
**BioCentury**

**WEEK IN REVIEW**

**POWERED BY BCIQ**

Molecular target: Janus kinase-2 (JAK-2); FMS-like tyrosine kinase 3 (FLT3) (CD135)

Description: Orally available dual inhibitor of Janus kinase-2 (JAK-2) and FMS-like tyrosine kinase 3 (FLT3; CD135)

Indication: Treat myelofibrosis (MF)

Endpoint: Percentage of patients with a ≥35% reduction in spleen volume as measured by MRI or CT at 24 weeks; percentage of patients with low platelet counts with a ≥35% reduction in spleen volume, symptom assessment scores, transfusions, hemoglobin count and quality of life (QOL)

Status: Phase III data

Milestone: Complete Phase III enrollment (mid-2015); submit NDA (year end 2015); submit MAA (2016)

Top-line data from the open-label, international Phase III PERSIST-1 in 327 patients with primary or secondary MF showed that once-daily 400 mg oral pacritinib met the primary endpoint of improving the percentage of patients with a ≥35% reduction in spleen volume as measured by MRI or CT from baseline to week 24 vs. best available therapy, excluding JAK-2 inhibitors (19.1% vs. 4.7%, p=0.0003). Additionally, pacritinib significantly improved the percentage of patients with a ≥35% reduction in spleen volume in the subgroups of patients with platelet counts of <100,000/µL and <50,000/µL vs. best available therapy. In 50 patients who were red blood cell transfusion dependent at study entry, a “clinically meaningful” percentage of patients receiving pacritinib became transfusion independent compared to best available therapy. The most common treatment-emergent adverse events reported were diarrhea, nausea and vomiting. PERSIST-1 enrolled patients with primary MF and post polycythemia vera/essential thrombocythemia MF (PPV-MF/PET-MF), without exclusion for low platelet counts.

The Phase III PERSIST-2 trial is evaluating twice-daily 200 mg pacritinib and once-daily 400 mg pacritinib vs. best available therapy, including approved JAK-1 and JAK-2 inhibitors, in about 300 patients with MF whose platelet counts are ≤100,000/µL. CTI expects to complete enrollment of PERSIST-2 in mid-2015. Under a 2013 deal, Baxter and CTI partnered to develop and commercialize pacritinib. Baxter received exclusive, worldwide rights to commercialize pacritinib, and the partners will jointly commercialize pacritinib in the U.S., where they will share costs and profits (see BioCentury, Nov. 13, 2013).

**Egalet Corp.** (NASDAQ:EGLT), Wayne, Pa.

Product: Egalet-001

Business: Neurology

Molecular target: Mu opioid receptor (MOR) (OPRM1)

Description: Abuse-deterrent, extended-release, oral formulation of morphine

Indication: Treat moderate to severe chronic pain

Endpoint: Bioequivalence based on area under the curve (AUC) and peak plasma (Cmax) concentrations

Status: Clinical trial data

Milestone: Start Clinical trial (03/2015); submit NDA (4Q15)

Top-line data from the open-label, crossover, pivotal bioequivalence Study 067-EG-012 in 63 healthy subjects showed that one 30 mg tablet and two 15 mg tablets of Egalet-001 each met the criteria for bioequivalence to a 30 mg MS Contin morphine sulfate controlled-release oral tablet based on AUC concentration and Cmax concentration. To demonstrate bioequivalence as defined by FDA, the 90% CI of the ratio for both parameters had to fall within 80-125% of the reference drug. The 30 mg tablet of Egalet-001 had an AUC ratio of 98.3% (90% CI: 96%, 100.7%) and a Cmax ratio of 98.6% (90% CI: 93.9%, 103.6%). The two 15 mg tablets of Egalet-001 had an AUC ratio of 98.4% (90% CI: 96.1%, 100.8%) and a Cmax ratio of 88% (90% CI: 83.9%, 92.4%). Egalet-001 was well tolerated with no serious adverse events reported. This month, Egalet plans to start a pivotal bioequivalence trial evaluating a 60 mg dose of Egalet-001. By year end, the company plans to submit an NDA to FDA for Egalet-001. **Purdue Pharma L.P.** (Stamford, Conn.) markets MS Contin.

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

Product: VT-464

Business: Cancer

Molecular target: Cytochrome P450 17 alpha-hydroxylase/C17, 20 lyase (CYP17) (CYP17A); Androgen receptor

Description: Non-steroidal dual androgen receptor antagonist and cytochrome P450 17 alpha-hydroxylase/C17, 20 lyase (CYP17; CYP17A) inhibitor

Indication: Treat castration-resistant prostate cancer (CRPC)

Endpoint: Safety; pharmacokinetics, objective tumor response using RECIST 1.1 criteria and change in prostate-specific antigen (KLK3; PSA) levels

Status: Interim Phase I/II data

Milestone: Phase I/II additional data (01/2016)

Interim data from 26 evaluable treatment-naïve patients with CRPC in an open-label, international Phase I/II trial showed that twice-daily 300-600 mg oral VT-464 led to PSA reductions in 19 patients. Of the 19 responders, 9 patients achieved a ≥30% reduction in PSA levels, 3 achieved a ≥50% reduction and 1 achieved a ≥90% reduction. Plasma testosterone concentrations were reduced to near or below the limit of quantification in most patients who received VT-464 at doses of ≥450 mg. No patients showed signs of adrenal insufficiency and no mineralocorticoid excess syndrome was reported. The trial is enrolling CRPC patients who were either treatment-naïve or had previously failed treatment with Xtandi enzalutamide or Zytiga abiraterone. Data were presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium in Orlando.
Keryx Biopharmaceuticals Inc. (NASDAQ:KERX), New York, N.Y.

Panion & BF Biotech Inc. (Taiwan:1760), Taipei, Taiwan

Japan Tobacco Inc. (Tokyo:2914), Tokyo, Japan

Torii Pharmaceutical Co. Ltd. (Tokyo:4551), Tokyo, Japan

Product: Auryxia ferric citrate (Riona) (KRX-0502, JTT-751) (formerly Zerenex)

Business: Endocrine/Metabolic

Description: Oral ferric iron-based phosphate binder

Indication: Treat hyperphosphatemia in patients with end-stage renal disease (ESRD)

Milestone: NA

Status: Additional Phase III data

Researchers at Rush University and colleagues reported data from a post hoc analysis of an open-label, international Phase III trial in 441 ESRD patients on hemodialysis or peritoneal dialysis showing that Auryxia reduced the risk of hospitalization by 24.2% vs. the active comparator of Renvela sevelamer carbonate and/or PhosLo calcium acetate (p=0.02). There were 181 unique hospitalizations in the Auryxia arm vs. 239 in control arm, for a total potential savings of $867,622 in hospitalization costs in the Auryxia arm. The researchers said that if the hospitalization reduction was applied to the general ESRD population, it would translate into a savings of $3,002 per patient per year. Hospitalization costs were estimated using the 2013 U.S. Renal Data System Annual Data Report. Data were published in Expert Review of Pharmacoeconomics & Outcomes Research. Keryx previously reported data from the trial showing that Auryxia met the primary endpoint of reducing mean serum phosphorus levels from week 52 to week 56 and safety; mean change in serum phosphorus concentration, ferritin levels, transferrin saturation (TSAT), use of IV iron and erythropoiesis-stimulating agents (ESAs) from baseline at day 0 to week 52

Status: Phase II data

Milestone: Start Phase II (2015)

Top-line data from an open-label, U.S. Phase II trial in 15 ambulatory patients showed that NSI-566 met the primary safety endpoint. NSI-566 was well tolerated with 1 patient experiencing a surgical serious adverse event. The maximum tolerated dose (MTD) was 16 million cells. On secondary endpoints, NSI-566 led to a response rate, defined as either a near zero slope of decline or a positive slope of ALSFRS score or positive strengthening of grip strength, of 47% at 9 months post-surgery. The average ALSFRS score was 37 points for responders and 14 points for non-responders at 9 months, corresponding to a 7% decline from baseline for responders vs. a 65% decline for non-responders. The average slope of decline of ALSFRS was 0.007 points per day for responders and 0.1 points per day for non-responders. Additionally, lung function as measured by seated vital capacity remained within 94% and 71% of baseline scores for responders and non-responders, respectively. The first 12 patients received injections of 1-8 million cells in the cervical region of the spinal cord and the final 3 patients received injections of 8 million cells into both the cervical and lumbar regions of the spinal cord. This summer, Neuralstem plans to start a larger Phase II trial in ALS patients.

ObsEva S.A., Geneva, Switzerland

Merck KGaA (Xetra:MRK), Darmstadt, Germany

Product: OBE001

Business: Genitourinary

Molecular target: Oxytocin (OXT) (OT)

Description: Oxytocin (OXT; OT) receptor antagonist

Indication: Prevent preterm labor

Endpoint: Safety and pharmacokinetics

Status: Phase I data

Milestone: NA

An open-label, crossover, French Phase I trial in 12 healthy, non-pregnant, post-menopausal women showed that once-daily 600 mg oral OBE001 alone and in combination with betamethasone for 2 days was well tolerated with headache and insomnia reported as the most common adverse events. Data were published in the Journal of Clinical Pharmacy and Therapeutics. ObsEva said it plans to start a Phase II trial of OBE001 to delay preterm labor, but did not disclose a time frame. ObsEva has exclusive, worldwide rights to OBE001 from Merck.

Neuralstem Inc. (NYSE-M:CUR), Rockville, Md.

Product: Human neural stem cells (hNSCs) (NSI-566, NSI-566RSC)

Business: Neurology

Molecular target: Not applicable

Description: Human neural stem cells (hNSCs)

Indication: Treat amyotrophic lateral sclerosis (ALS)

Endpoint: Safety, ALS Functional Rating Scale (ALSFRS) and positive strengthening of grip strength

ObsEva said it plans to start a

Analysis of an open-label, international Phase III trial in 14 positive strengthening of grip strength

Endpoint: Safety; ALS Functional Rating Scale (ALSFRS) and Indication: Treat amyotrophic lateral sclerosis (ALS)

Description: Human neural stem cells (hNSCs)

Molecular target: Not applicable

Business: Neurology

Product: Human neural stem cells (hNSCs) (NSI-566, NSI-566RSC)

Neuralstem Inc. (Tokyo:2914), Tokyo, Japan

Torii Pharmaceutical Co. Ltd. (Tokyo:4551), Tokyo, Japan

Product: Auryxia ferric citrate (Riona) (KRX-0502, JTT-751) (formerly Zerenex)

Business: Endocrine/Metabolic

Description: Oral ferric iron-based phosphate binder

Indication: Treat hyperphosphatemia in patients with end-stage renal disease (ESRD)

Milestone: NA

Status: Additional Phase III data

Researchers at Rush University and colleagues reported data from a post hoc analysis of an open-label, international Phase III trial in 441 ESRD patients on hemodialysis or peritoneal dialysis showing that Auryxia reduced the risk of hospitalization by 24.2% vs. the active comparator of Renvela sevelamer carbonate and/or PhosLo calcium acetate (p=0.02). There were 181 unique hospitalizations in the Auryxia arm vs. 239 in control arm, for a total potential savings of $867,622 in hospitalization costs in the Auryxia arm. The researchers said that if the hospitalization reduction was applied to the general ESRD population, it would translate into a savings of $3,002 per patient per year. Hospitalization costs were estimated using the 2013 U.S. Renal Data System Annual Data Report. Data were published in Expert Review of Pharmacoeconomics & Outcomes Research. Keryx previously reported data from the trial showing that Auryxia met the primary endpoint of reducing mean serum phosphorus levels from week 52 to week 56 and safety; mean change in serum phosphorus concentration, ferritin levels, transferrin saturation (TSAT), use of IV iron and erythropoiesis-stimulating agents (ESAs) from baseline at day 0 to week 52

Status: Phase II data

Milestone: Start Phase II (2015)

Top-line data from an open-label, U.S. Phase II trial in 15 ambulatory patients showed that NSI-566 met the primary safety endpoint. NSI-566 was well tolerated with 1 patient experiencing a surgical serious adverse event. The maximum tolerated dose (MTD) was 16 million cells. On secondary endpoints, NSI-566 led to a response rate, defined as either a near zero slope of decline or a positive slope of ALSFRS score or positive strengthening of grip strength, of 47% at 9 months post-surgery. The average ALSFRS score was 37 points for responders and 14 points for non-responders at 9 months, corresponding to a 7% decline from baseline for responders vs. a 65% decline for non-responders. The average slope of decline of ALSFRS was 0.007 points per day for responders and 0.1 points per day for non-responders. Additionally, lung function as measured by seated vital capacity remained within 94% and 71% of baseline scores for responders and non-responders, respectively. The first 12 patients received injections of 1-8 million cells in the cervical region of the spinal cord and the final 3 patients received injections of 8 million cells into both the cervical and lumbar regions of the spinal cord. This summer, Neuralstem plans to start a larger Phase II trial in ALS patients.

ObsEva S.A., Geneva, Switzerland

Merck KGaA (Xetra:MRK), Darmstadt, Germany

Product: OBE001

Business: Genitourinary

Molecular target: Oxytocin (OXT) (OT)

Description: Oxytocin (OXT; OT) receptor antagonist

Indication: Prevent preterm labor

Endpoint: Safety and pharmacokinetics

Status: Phase I data

Milestone: NA

An open-label, crossover, French Phase I trial in 12 healthy, non-pregnant, post-menopausal women showed that once-daily 600 mg oral OBE001 alone and in combination with betamethasone for 2 days was well tolerated with headache and insomnia reported as the most common adverse events. Data were published in the Journal of Clinical Pharmacy and Therapeutics. ObsEva said it plans to start a Phase II trial of OBE001 to delay preterm labor, but did not disclose a time frame. ObsEva has exclusive, worldwide rights to OBE001 from Merck.

Neuralstem Inc. (NYSE-M:CUR), Rockville, Md.

Product: Human neural stem cells (hNSCs) (NSI-566, NSI-566RSC)

Business: Neurology

Molecular target: Not applicable

Description: Human neural stem cells (hNSCs)

Indication: Treat amyotrophic lateral sclerosis (ALS)

Endpoint: Safety, ALS Functional Rating Scale (ALSFRS) and positive strengthening of grip strength
Endpoint: Absence of cells in anterior chamber of the study eye at day 14 and absence of pain at day 8; absence of cells in anterior chamber of the study eye and absence of pain at days 2, 4, 14 and 30
Status: Phase III data
Milestone: Phase IIIb data (03/2015); submit NDA (2Q15)

Top-line data from a double-blind, U.S. Phase IIIa trial in 247 patients undergoing cataract surgery showed that OTX-DP met the co-primary endpoints of reducing inflammation as measured by the proportion of patients with absence of inflammatory cells in the anterior chamber of the study eye at day 14 (33.7% vs. 14.6%, p=0.0015) and absence of pain at day 8 (76.1% vs. 36.1%, p<0.0001) vs. a placebo control punctum plug. Top-line data from a Phase IIIb trial of OTX-DP in 240 patients undergoing cataract surgery are expected this month. The plug, which uses the company’s polyethylene glycol hydrogel technology and includes a visualization agent, is designed to degrade and exit through the nasolacrimal system without the need for removal by a physician at the end of treatment.

Oryx GmbH & Co. KG, Baldham, Germany
Product: VicOryx
Business: Cancer
Molecular target: Cyclin dependent kinase inhibitor 2A (CDKN2A) (INK4a) (ARF) (p16INK4a)
Description: Vaccine comprised of a synthetic cyclin dependent kinase inhibitor 2A (CDKN2A; INK4a; ARF; p16INK4a) peptide
Indication: Treat HPV-associated cancers
Endpoint: Cellular and humoral immune responses; safety and tumor response according to RECIST criteria
Status: Phase I/IIa data
Milestone: NA

An open-label, German Phase I/IIa trial in 26 patients with p16INK4a-overexpressing HPV-positive cancer showed that once-weekly subcutaneous 100 µg VicOryx plus the Montanide ISA 51 VG adjuvant for the first 4 weeks of an 8-week cycle was safe and induced humoral and cellular immune responses.

Oryx GmbH & Co. KG, Baldham, Germany
Product: MicOryx
Business: Cancer
Molecular target: NA
Description: Vaccine comprised of 3 synthetic frameshift peptides: AIM2, HT001 and TAF1B
Indication: Treat advanced microsatellite unstable (MSI-H) colorectal cancer
Endpoint: Safety (Phase I) and cellular and humoral immune responses (Phase IIa)
Status: Phase I/IIa data
Milestone: NA

An open-label Phase I/IIa trial in 22 patients with advanced MSI-H colorectal cancer who received standard chemotherapy showed that MicOryx was safe and induced humoral and cellular immune responses.

Progenics Pharmaceuticals Inc. (NASDAQ: PGNX), Tarrytown, N.Y.
Product: PSMA ADC
Business: Cancer
Molecular target: Prostate-specific membrane antigen (PSMA) (FOLH1) (GCPII)
Description: Antibody-drug conjugate (ADC) composed of a human mAb against prostate-specific membrane antigen (PSMA; FOLH1; GCPII) and monomethyl auristatin E (MMAE)
Indication: Treat metastatic castration-resistant prostate cancer (CRPC)
Endpoint: Change in tumor assessments according to RECIST 1.1 criteria and changes in levels of serum prostate-specific antigen (KLK3; PSA) and circulating tumor cells (CTCs); bone, visceral and nodal metastases, pain and safety
Status: Additional Phase II data
Milestone: NA

Data from 91 evaluable patients with metastatic CRPC in the open-label, U.S. Phase II PSMA ADC 2301 trial showed that 2.3 and 2.5 mg/kg IV PSMA ADC given every 3 weeks for up to 8 cycles led to 1 complete response and 5 partial responses, plus 72 cases of stable disease. Additionally, PSMA ADC reduced levels of CTCs by ≥50% in 60 of 77 (78%) patients and reduced PSA levels by ≥30% in 34 of 113 (30%) patients and by ≥50% in 16 of 113 (14%) patients. In 29 evaluable chemotherapy-naïve patients who have progressed on hormonal therapies, PSMA ADC led to 1 complete response and 4 partial responses, plus 22 cases of stable disease. In chemotherapy-naïve patients, PSMA ADC reduced levels of CTCs by ≥50% in 17 of 19 (89%) patients and reduced PSA levels by ≥30% in 11 of 34 (32%) patients and by ≥50% in 7 of 34 (21%) patients.

The trial enrolled 119 patients with metastatic CRPC who progressed despite treatment with Zytiga abiraterone and/or Xtandi enzalutamide, including 84 taxane-experienced patients and 35 chemotherapy-naïve patients. Data were presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium in Orlando. Progenics previously reported data from 50 evaluable CRPC patients (see BioCentury, Feb. 3, 2014 & June 23, 2014). PSMA ADC uses ADC technology from Seattle Genetics Inc. (NASDAQ: SGEN, Bothell, Wash.).

R-Tech Ueno Ltd. (JASDAQ: 4573), Tokyo, Japan
Product: Unoprostone isopropyl (Rescula) (UF-021)
Business: Ophthalmic
Molecular target: Potassium channel KCa1.1 (KCNMA1) (SLO); Chloride channel 2 (CLCN2) (CIC-2)
Description: Docosanoid-type prostone
Indication: Treat retinitis pigmentosa (RP)
Week of March 16, 2015

WEEK IN REVIEW

**Symbiomix Therapeutics LLC**, Newark, N.J.
Product: Secnidazole (SYM-1219)
Business: Infectious
Molecular target: NA
Description: 5-nitroimidazole antibiotic
Indication: Treat bacterial vaginosis
Endpoint: Safety and pharmacokinetics
Status: Phase I data
Milestone: Submit NDA (mid-2016)

An open-label Phase I trial in 28 healthy female volunteers showed that single doses of 1 and 2 g oral SYM-1219 were well tolerated with headache and nausea reported as the most common adverse events. Data were presented at the American Society of Clinical Pharmacology and Therapeutics meeting in New Orleans. Symbiomix said it has completed a Phase II trial of SYM-1219 in women with bacterial vaginosis and the company plans to submit an NDA to FDA for the product in mid-2016.

**Themis Bioscience GmbH**, Vienna, Austria
Product: MV-CHIK vaccine
Business: Infectious
Molecular target: NA
Description: Vaccine developed using Thermaxyn technology that uses a single measles virus vector expressing the chikungunya E1 and E2 proteins
Indication: Prevent chikungunya virus infection
Endpoint: Presence of neutralizing anti-chikungunya antibodies on day 28; safety
Status: Additional Phase I data
Milestone: NA

Additional data from a double-blind, placebo-controlled, Austrian Phase I trial in 42 healthy adults ages 18-45 showed that MV-CHIK led to seroconversion rates of 44% in the low-dose group, 92% in the mid-dose group and 90% in the high-dose group after the first immunization. The seroconversion rate was 100% for all vaccine groups after a second booster immunization on day 28 or 90. No vaccination-related serious adverse events were reported. Data were published in *The Lancet Infectious Diseases*. Themis previously reported interim data from the trial (see BioCentury, Aug. 4, 2014). The company said it plans to move the vaccine into Phase II testing, but did not provide details.

**Vanda Pharmaceuticals Inc.**, (NASDAQ:VNDA), Washington, D.C.
Eli Lilly and Co., (NYSE:LLY), Indianapolis, Ind.
Product: Tradipitant (formerly LY686017, VLY-686)
Business: Dermatology
Molecular target: Neurokinin 1 (NK1) Substance P receptor (TACR1)
Description: Neurokinin 1 (NK1) receptor antagonist
Indication: Treat chronic pruritus in atopic dermatitis
Endpoint: Change from baseline in visual analog scale (VAS) for itch at week 4; verbal rating scale (VRS), atopic dermatitis skin lesions using SCORAD (SCORing Atopic Dermatitis Index), Patient Benefit Index (PBI) and Clinical Global Impression of Change (CGI-C)
Status: Phase II data

**Symbiomix Therapeutics LLC**, Newark, N.J.
Product: Secnidazole (SYM-1219)
Business: Infectious
Molecular target: NA
Description: 5-nitroimidazole antibiotic
Indication: Treat bacterial vaginosis
Endpoint: Safety and pharmacokinetics
Status: Phase III data

Top-line data from a double-blind, Japanese Phase III trial in about 180 patients showed that 0.15% unoprostone isopropyl eye drops missed the primary endpoint of improving mean retinal sensitivity at 4 central points from baseline to 1 year vs. placebo. Based on the data, R-Tech closed the 52-week open-label extension of the trial. Following an analysis of the data, *Sucampo Pharmaceuticals Inc.* (NASDAQ:SCMP, Bethesda, Md.) returned all rights to unoprostone isopropyl to R-Tech. Last year, Sucampo ceased marketing of Rescula unoprostone isopropyl, which is approved to treat open-angle glaucoma or ocular hypertension (see BioCentury, March 2). Sucampo had exclusive rights from R-Tech to develop and commercialize Rescula worldwide outside of Japan, Korea, Taiwan and China under an amended 2009 deal.
Top-line data from the double-blind, German Phase II VP-VLY-686-2101 trial in 69 atopic dermatitis patients with chronic pruritus showed that once-daily 100 mg oral tradipitant given in the evening missed the primary endpoint of improving VAS scores for itch from baseline to week 4 vs. placebo. Vanda said there were no significant differences observed between the treatment groups due to a high placebo effect. Specifically, tradipitant improved the endpoint by 40.5 mm from baseline to week 4 vs. 36.5 mm for placebo (p=0.0001 for both compared to baseline).

Vanda said that a PK-PD analysis of the tradipitant arm showed a significant correlation between blood levels of the product and the change in VAS score (p<0.05). Additionally, patients who were assessed in the morning, about 12 hours post-dose, had higher blood levels of tradipitant than patients who were assessed in the afternoon, about 18 hours post-dose. In patients who were assessed in the morning (n=35), tradipitant significantly improved VAS (reduction of 54 mm vs. a reduction of 30.3 mm, p<0.01), VRS (reduction of 1.46 points vs. a reduction of 0.67 points, p<0.05), CGI-C (2.46 vs. 3.61 points, p<0.05), PBI (1.47 vs. 0.73 points, p<0.05) and atopic dermatitis skin lesions as measured by SCORAD (reduction of 9.58 points vs. a reduction of 4.36 points, p<0.01) vs. placebo. In patients who were assessed in the afternoon, there were no significant differences between treatment arms. Tradipitant was well tolerated. In 2012, Eli Lilly granted Vanda exclusive, worldwide rights to develop and commercialize tradipitant (see BioCentury, April 23, 2012).

**ViroMed Co. Ltd.** (KOSDAQ:084990), Seoul, South Korea

**Product:** VM202  
**Business:** Neurology  
**Molecular target:** NA  
**Description:** PCK vector encoding the engineered hepatocyte growth factor (HGF) gene  
**Indication:** Treat diabetic peripheral neuropathy (DPN)  
**Endpoint:** Change from baseline in mean 24-hour pain score as measured by mean daily pain and sleep interference diary; Michigan Neuropathy Screening Instrument (MNSI) score, Brief Pain Inventory-Short Form (BPI-SF), visual analog scale (VAS), Patient Global Impression of change (PGI-C) and safety  
**Status:** Phase II data  
**Milestone:** NA

A double-blind, U.S. and Korean Phase II trial in 84 evaluable patients with DPN showed that 8 and 16 mg intramuscular VM202 per leg led to reductions in mean 24-hour pain score as measured by mean daily pain and sleep interference diary of 3.03 and 1.9 points, respectively, from baseline to day 90 vs. a reduction of 1.57 points for placebo (p=0.038 and p=0.758, respectively). Low- and high-dose VM202 led to mean pain reductions of 2.78 and 1.94 points, respectively, from baseline to 6 months vs. a reduction of 1.59 points for placebo (p=0.099 and p=0.761, respectively). At 9 months, low- and high-dose VM202 led to mean pain reductions of 2.98 and 2.01 points, respectively, vs. a reduction of 1.95 points for placebo (p=0.239 and p=0.994, respectively).

Additionally, low- and high-dose VM202 led to responder rates, defined as patients who achieved a ≥50% reduction in mean pain from baseline, of 48.4% and 27.8%, respectively, at day 90 vs. 17.6% for placebo (p=0.06 for low-dose VM202 vs. placebo). Low- and high-dose VM202 led to responder rates of 38.7% and 25%, respectively, at 6 months vs. 17.6% for placebo. At 9 months, low- and high-dose VM202 led to responder rates of 41.9% and 28.6%, respectively, vs. 25% for placebo. VM202 was well tolerated. Data were published in the *Annals of Clinical and Translational Neurology*.

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

**Product:** XOMA 358  
**Business:** Endocrine/Metabolic  
**Molecular target:** Insulin receptor (INSR)  
**Description:** Allosteric human IgG2 mAb that binds to insulin receptor (INSR)  
**Indication:** Treat endogenous hyperinsulinemic hypoglycemia  
**Endpoint:** Safety and pharmacokinetics; change from baseline in insulin, C-peptide and post-prandial glucose levels  
**Status:** Phase I data  
**Milestone:** NA

A double-blind, placebo-controlled, U.S. Phase I trial in 19 healthy male volunteers showed that single doses of 0.1, 0.3, 1 and 3 mg/kg IV XOMA 358 were well tolerated with no severe adverse events reported. Additionally, XOMA 358 led to dose-related increases in post-prandial glucose levels that were consistent with down-regulation of insulin signaling through day 6 following infusion. Furthermore, the day 3 glucose area under the curve (AUC) for the 1 mg/kg dose of XOMA 358 was about 80% greater than placebo. Data were presented at the Endocrine Society meeting in San Diego.
p<0.05). Data were published in *PLoS ONE*. Last year, BioLineRx granted JHL exclusive rights to develop and commercialize the mAb inhibitor of natural cytotoxicity triggering receptor 1 (NCR1; NKP46; CD335) in China and Southeast Asia, as well as worldwide manufacturing rights (see BioCentury, Jan. 20, 2014).

**CLINICAL NEWS**

**CLINICAL STATUS**

**Aduro Biotech Inc., Berkeley, Calif.**

Product: CRS-207  
Business: Cancer  
Molecular target: NA  
Description: Live attenuated strain of *Listeria monocytogenes* that expresses human mesothelin  
Indication: Treat pancreatic cancer  
Endpoint: Overall survival (OS), progression-free survival (PFS), immune-related PFS, time to progression, response rate and pharmacokinetics  
Status: Phase II started  
Milestone: NA  
The Sidney Kimmel Comprehensive Cancer Center began the open-label, U.S. Phase II STELLAR trial to compare Aduro’s GVAX Pancreas cancer vaccine plus its IV CRS-207 in combination with Opdivo nivolumab from *Bristol-Myers Squibb Co.* (NYSE:BMY, New York, N.Y.) vs. GVAX Pancreas plus CRS-207 alone in 88 patients with metastatic pancreatic cancer patients who have received 1 prior chemotherapy regimen. Patients will receive 6 intradermal injections of GVAX Pancreas on day 1 of cycles 1 and 2, followed by IV CRS-207 on day 1 or 2 of cycles 3-6, with or without Opdivo on day 1 of each cycle. All patients will also receive low-dose cyclophosphamide. The combination of CRS-207 and GVAX Pancreas has breakthrough therapy designation from FDA to treat pancreatic cancer. Stand Up to Cancer (SU2C), Pancreatic Cancer Action Network and BMS are supporting the trial. Aduro is also evaluating CRS-207 plus GVAX Pancreas and low-dose cyclophosphamide in the Phase IIb ECLIPSE trial to treat pancreatic cancer. CRS-207 is a live attenuated strain of *Listeria monocytogenes* that expresses human mesothelin.

**Aduro Biotech Inc., Berkeley, Calif.**

Product: GVAX Pancreas cancer vaccine  
Business: Cancer  
Molecular target: NA  
Description: Allogeneic cancer vaccine engineered to secrete GM-CSF  
Indication: Treat pancreatic cancer  
Endpoint: Overall survival (OS), progression-free survival (PFS), immune-related PFS, time to progression, response rate and pharmacokinetics  
Status: Phase II started  
Milestone: NA  
The Sidney Kimmel Comprehensive Cancer Center began the open-label, U.S. Phase II STELLAR trial to compare Aduro’s GVAX Pancreas cancer vaccine plus its IV CRS-207 in combination with Opdivo nivolumab from *Bristol-Myers Squibb Co.* (NYSE:BMY, New York, N.Y.) vs. GVAX Pancreas plus CRS-207 alone in 88 patients with metastatic pancreatic cancer patients who have received 1 prior chemotherapy regimen. Patients will receive 6 intradermal injections of GVAX Pancreas on day 1 of cycles 1 and 2, followed by IV CRS-207 on day 1 or 2 of cycles 3-6, with or without Opdivo on day 1 of each cycle. All patients will also receive low-dose cyclophosphamide. The combination of CRS-207 and GVAX Pancreas has breakthrough therapy designation from FDA to treat pancreatic cancer. Stand Up to Cancer (SU2C), Pancreatic Cancer Action Network and BMS are supporting the trial. Aduro is also evaluating CRS-207 plus GVAX Pancreas and low-dose cyclophosphamide in the Phase IIb ECLIPSE trial to treat pancreatic cancer. GVAX Pancreas is an allogeneic cancer vaccine engineered to secrete GM-CSF.

**AOP Orphan Pharmaceuticals AG, Vienna, Austria**

Product: PEG-P-INF alfa-2b, Ropeginterferon alfa 2b (AOP2014, P1101)  
Business: Hematology  
Molecular target: NA  
Description: Long-acting pegylated interferon (IFN) alfa-2b  
Indication: Treat polycythemia vera (PV)  
Endpoint: Composite endpoint of hematocrit, platelets, leukocytes and spleen size at 12 months; disease response at 3, 6 and 9 months, Janus kinase-2 (JAK-2) allelic burden changes, time to response, duration of response, number of phlebotomies, blood parameters, spleen size, disease-related symptoms and safety  
Status: Completed Phase III enrollment  
Milestone: Phase III final data (1H16)  
AOP completed enrollment of >260 patients in the open-label, European Phase III PROUD-PV trial comparing 50-500 µg subcutaneous ropeginterferon alfa-2b every other week vs. oral hydroxyurea once daily or every other day for 1 year. PharmaEssentia said FDA agreed that data from PROUD-PV can be used as part of a BLA submission. AOP has rights to develop and commercialize the product for myeloproliferative disorders in central Europe, the Commonwealth of Independent States and the Middle East from PharmaEssentia.

**Defyrus Inc., Toronto, Ontario**

Product: Zmapp  
Business: Infectious
Molecular target: NA
Description: Combination of 3 mAbs targeting Ebola glycoproteins GP1 and GP2
Indication: Treat Ebola infection
Endpoint: Mortality at 28 days; clinical and virology effects, safety and plasma viral load
Status: Phase I/II started
Milestone: Complete Phase I/II (12/2016)
NIH’s National Institute of Allergy and Infectious Diseases (NIAID) began an open-label, U.S. and Liberian Phase I/II trial to compare IV ZMapp every 3 days for 3 doses vs. standard of care (SOC). NIAID said if the trial does not find a “significant difference” in the ZMapp vs. SOC portion, it may go on to enroll additional patients to evaluate other experimental Ebola therapies. SOC includes providing IV fluids, balancing electrolytes, maintaining oxygen status and blood pressure and treating other infections. ZMapp combines components of mAbs targeting Ebola glycoproteins GP1 and GP2. Mapp licensed 2 of the mAbs from Defyrus.

**Endo International plc** (NASDAQ:ENDP; TSX:ENL), Dublin, Ireland
**Trevi Therapeutics Inc.**, New Haven, Conn.

**Product:** Nalbuphine ER (T111)
**Business:** Dermatology
Molecular target: Mu opioid receptor (MOR) (OPRM1); Kappa opioid receptor (KOR) (OPRK1)
Description: Extended-release oral formulation of nalbuphine, a mu opioid receptor (OPRM1; MOR) antagonist and kappa opioid receptor (OPRK1; KOR) agonist
Indication: Treat prurigo nodularis
Endpoint: Change from baseline in the worst itch Numerical Rating Scale (NRS); patient perception of burden of itch, quality of life (QOL) effects of pruritus and effect on sleep, anxiety and depression
Status: Phase II/III started
Milestone: Phase II/III data (3Q15)
Trevi began a double-blind, placebo-controlled, international Phase II/III trial to evaluate 90 and 180 mg oral Nalbuphine ER twice daily for 8 weeks in about 60 patients with moderate to severe itch. The trial includes a 1-year open-label extension. Trevi has exclusive, worldwide rights to the compound from Endo.

**Galmed Pharmaceuticals Ltd.** (NASDAQ:GLMD), Tel Aviv, Israel

**Product:** Aramchol arachidyl amino cholanoic acid
**Business:** Hepatic
Molecular target: Stearoyl-CoA desaturase-1 (SCD1)
Description: Synthetic conjugate of cholic acid and arachidic acid
Indication: Treat non-alcoholic steatohepatitis (NASH)
Endpoint: Reduction of liver fat content measured by magnetic resonance spectroscopy (MRS) and safety; complete resolution of NASH, non-alcoholic fatty liver disease (NAFLD) activity score (NAS) and changes in alanine aminotransferase (ALT), insulin resistance, HbA1C, adiponectin, leptin/adiponectin ratio (LAR) and biomarkers of inflammation and fibrosis
Status: Phase IIb started
Milestone: Phase IIb interim data (IH16); Phase IIb data (year end 2016)
Galmed began the double-blind, placebo-controlled, dose-ranging, international Phase IIb ARREST trial to evaluate 400 and 600 mg oral Aramchol once daily for 52 weeks in about 240 overweight or obese patients with insulin resistance.

**Heat Biologics Inc.** (NASDAQ:HTBX), Chapel Hill, N.C.

**Product:** Vesigenurtacel-L (HS-410)
**Business:** Cancer
Molecular target: Heat shock 90 kDa protein beta 1 (Hsp90B1) (GP96) (GRP94)
Description: Bladder cancer cell line genetically modified using Immune Pan-Antigen Cytotoxic Therapy (ImPACT) technology to secrete bladder cancer antigens bound to a heat shock 90 kDa protein beta 1 (Hsp90B1; GP96; GRP94) adjuvant
Indication: Treat non-muscle invasive bladder cancer
Endpoint: Safety and immune response (Phase I) and 1-year disease-free survival (DFS) (Phase II); proportion of patients with recurrence and progressive disease at 6, 12, 18 and 24 months, DFS and overall survival (OS)
Status: Phase I/II amended
Milestone: Complete Phase II enrollment (year end 2015)
Heat Biologics amended a U.S. Phase I/II trial of HS-410 to add an open-label arm to the Phase II portion evaluating the compound as a monotherapy in an additional 25 patients. The double-blind Phase II portion is enrolling about 75 patients who have undergone transurethral resection of bladder tumor to receive placebo or 1*106 and 1*107 cells/dose HS-410 weekly given in combination with bacillus Calmette-Guerin (BCG) for 6 weeks, then alone for 6 additional weeks followed by 3 courses of the combination weekly for 3 weeks at 3, 6 and 12 months after starting therapy. The open-label Phase I portion enrolled 10 patients to receive BCG for 5-6 weeks, followed by 1*106 cells/dose HS-410 weekly for 12 weeks and then monthly for 3 months. Heat said the decision to add the arm occurred after observing a vaccine-induced immune response in the Phase I portion (see BioCentury, Feb. 16).
Heat plans to complete enrollment in the double-blind arms by 3Q15 and in the monotherapy arm by year end. FDA also granted Fast Track designation to HS-410 in combination with BCG to treat non-muscle invasive bladder cancer.
**Isis Pharmaceuticals Inc.** (NASDAQ:ISIS), Carlsbad, Calif.

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

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

**Sumitomo Dainippon Pharma Co. Ltd.** (Tokyo:4506), Osaka, Japan

**Trevena Inc.** (NASDAQ:TRVN), King of Prussia, Pa.

**VistaGen Therapeutics Inc.** (OTCQB:VSTA), South San Francisco, Calif.

**Milestone:** Phase II data (year end 2015); submit NDA (1Q16)

**Description:** Oral inhibitor of HER1, HER2 and HER4 kinases

**Indication:** Extended adjuvant treatment of HER2-positive breast cancer

**Business:** Cancer

**Product:** Oral neratinib (HKI-272, PB272)

**Status:** Phase II start

**Endpoint:** Reduction in incidence and severity of diarrhea

**Indication:** Treat major depressive disorder (MDD)

**Business:** Neurology

**Product:** Glycopyrrolate bromide (SUN-101) (formerly EP-101)

**Status:** Phase II start
Milestone: Start Phase II (2Q15); Phase II data (year end 2015)
Next quarter, VistaGen said NIH's National Institute of Mental Health (NIMH) will begin a double-blind, placebo-controlled, crossover, U.S. Phase II trial to evaluate 1,440 mg oral AV-101 once daily for 14 days in about 25 patients.
**Financial News**

**Completed Offerings**

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Business Description</th>
<th>Date Completed</th>
<th>Type</th>
<th>Raised</th>
<th>Shares</th>
<th>Price</th>
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</thead>
<tbody>
<tr>
<td><strong>Addex Therapeutics Ltd.</strong> (SIX:ADXN), Geneva, Switzerland</td>
<td>Neurology, Autoimmune, Endocrine/Metabolic</td>
<td>2015-03-09</td>
<td>Private placement</td>
<td>CHF2.8 million ($2.8 million)</td>
<td>921,667</td>
<td>CHF3</td>
<td>Herculis Partners; company management</td>
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<tr>
<td><strong>ADMA Biologics Inc.</strong> (NASDAQ:ADMA), Ramsey, N.J.</td>
<td>Hematology, Infectious</td>
<td>2015-03-13</td>
<td>Follow-on</td>
<td>$9.8 million</td>
<td>1.2 million</td>
<td>$8</td>
<td>Raymond James; Laidlaw; Maxim Group</td>
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<tr>
<td><strong>Allergen Research Corp.</strong></td>
<td>Inflammation</td>
<td>2015-03-12</td>
<td>Venture financing</td>
<td>$80 million</td>
<td></td>
<td></td>
<td>Foresite Capital; Longitude Capital Management; Fidelity; Aisling Capital; Adage Capital Management; Rock Springs Capital; EcoR1 Capital; Eventide Asset Management; Aperture Venture Partners; Longitude Capital Management; Skyline Ventures; Frazier Healthcare; Boston Millennia Partners</td>
</tr>
<tr>
<td><strong>AmpliPhi Biosciences Corp.</strong> (OTCBB:APHB), Richmond, Va.</td>
<td>Infectious</td>
<td>2015-03-10</td>
<td>Private placement</td>
<td>$13 million</td>
<td>78.8 million</td>
<td>$0.17</td>
<td>Intrexon Corp.; new investors; existing investors</td>
</tr>
<tr>
<td><strong>Collegium Pharmaceutical Inc.</strong></td>
<td>Drug delivery, Neurology, Inflammation</td>
<td>2015-03-10</td>
<td>Venture financing</td>
<td>$50 million</td>
<td>1.2 million</td>
<td>$8</td>
<td>TPG Biotech; RA Capital Management; Adage Capital Management; Rock Springs Capital; EcoR1 Capital; Eventide Asset Management; Aperture Venture Partners; Longitude Capital Management; Skyline Ventures; Frazier Healthcare; Boston Millennia Partners</td>
</tr>
<tr>
<td><strong>Galena Biopharma Inc.</strong> (NASDAQ:GALE), Portland, Ore.</td>
<td>Cancer</td>
<td>2015-03-13</td>
<td>Follow-on</td>
<td>$38 million</td>
<td>24.4 million</td>
<td>$1.56</td>
<td>Raymond James; Roth Capital Partners; Maxim Group; MLV; Noble Life Science Partners</td>
</tr>
<tr>
<td><strong>Genocea Biosciences Inc.</strong> (NASDAQ:GNCA), Cambridge, Mass.</td>
<td>Infectious</td>
<td>2015-03-12</td>
<td>Follow-on</td>
<td>$45 million</td>
<td>5.5 million</td>
<td>$8.25</td>
<td>Cowen; Piper Jaffray; Stifel, Nicolaus; Needham</td>
</tr>
</tbody>
</table>

Note: Investors received five-year warrants to purchase up to 19.7 million shares at $0.22.

**Week ended 3/13/15. Shares after offering refers to shares outstanding. Proceeds are gross, not net. Shares offered don't include overallotments. Currency rates used in the week: CHF=$1.0147; €=$1.0855; £=$1.5129; NOK=$0.126**
GrayBug Inc., Baltimore, Md.
Business: Drug delivery, Ophthalmic
Date completed: 2015-03-10
Type: Venture financing
Raised: $1.7 million
Investors: Hatteras Funds; Maryland Venture Fund
Note: The financing is a series A-2 round.

Heat Biologics Inc. (NASDAQ:HTBX), Chapel Hill, N.C.
Business: Cancer, Inflammation, Infectious
Date completed: 2015-03-10
Type: Follow-on
Raised: $10.7 million
Shares: 1.6 million
Price: $6.50
Shares after offering: 8.1 million
Underwriters: Aegis Capital; H.C. Wainwright
Overallotment: 246,000

Inflection Biosciences Ltd., Blackrock, Ireland
Business: Cancer
Date completed: 2015-03-09
Type: Venture financing
Raised: €725,000 ($786,988)
Investors: New investors; existing investors
Note: The financing includes the conversion of €225,000 ($244,238) in previously issued loan notes.

Kura Oncology Inc., La Jolla, Calif.
Business: Cancer
Date completed: 2015-03-12
Type: Venture financing
Raised: $60 million
Placement agents: Leerink; National Securities; Livingston Securities
Investors: EcoR1 Capital; Fidelity; Arch Venture Partners; Partner Fund Management; Tavistock Life Sciences; Nextech Invest; institutional investors; existing investors
Note: The amount raised includes $7.5 million in bridge funding, which converted into common stock. In conjunction with the offering, Kura reversed-merged with Zeta Acquisition Corp. III, a public reporting company. Kura will seek to list its shares on an OTC exchange.

Kythera Biopharmaceuticals Inc. (NASDAQ:KYTH), Calabasas, Calif.
Business: Dermatology
Date completed: 2015-03-10
Type: Follow-on
Raised: $125 million
Shares: 2.6 million
Price: $48
Shares after offering: 25.3 million
Underwriters: Goldman Sachs; BofA Merrill Lynch; Leerink Partners; Cowen
Overallotment: 390,625

Business: Neurology
Date completed: 2015-03-13
Type: Private placement of common stock and warrants
Raised: $31 million
Shares: 6.3 million
Price: $4.81
Shares after offering: 24.7 million
Investor: Institutional investors
Note: Minerva raised $30.2 million through the sale of 6.3 million shares at $4.81 and $785,208 through the sale of 6.3 million warrants at $0.13 per warrant. Each warrant is exercisable at $5.77.

Business: Drug delivery, Biomanufacturing
Date completed: 2015-03-12
Type: Venture financing
Raised: $40 million
Investors: AstraZeneca plc; New Enterprise Associates; Hatteras Venture Partners; Johnson & Johnson Development Corp.; Fletcher Spaght Ventures

Portola Pharmaceuticals Inc. (NASDAQ:PTLA), South San Francisco, Calif.
Business: Cardiovascular, Cancer, Hematology
Date completed: 2015-03-10
Type: Follow-on
Raised: $99.8 million
Shares: 2.5 million
Price: $40
Shares after offering: 51.3 million
Underwriters: Morgan Stanley; Credit Suisse; Cowen; Sanford C. Bernstein
Overallotment: 374,348

TapImmune Inc. (OTCBB:TPIV), Seattle, Wash.
Business: Cancer, Infectious
Date completed: 2015-03-10
Type: Private placement of units
Raised: $1 million
Units: 5 million
Price: $0.20 (unit)
Shares after offering: 32.6 million
Investor: Eastern Capital
Note: Each unit comprises a share; a five-year series A warrant to purchase a share at $1.50; a six-month series B warrant to purchase a share at $0.40; a five-year series C warrant to purchase a share at $1; a series D warrant to purchase a share at $0.75; and a series E warrant to purchase a share at $1.25.

**Tetraphase Pharmaceuticals Inc.** (NASDAQ:TTPH), Watertown, Mass.
Business: Infectious
Date completed: 2015-03-11
Type: Follow-on
Raised: $150.5 million
Shares: 4.3 million
Price: $35
Shares after offering: 35.3 million
Underwriters: BMO Capital Markets; Stifel, Nicolaus; Guggenheim Securities; Nomura; SunTrust
Over allotment: 645,000

**Tobira Therapeutics Inc.**, San Francisco, Calif.
Business: Infectious
Date completed: 2015-03-09
Type: Venture financing
Raised: $13 million
Investors: Abingworth Management; Biotechnology Value Fund; Stonepine Capital; existing investors
Note: The offering is convertible notes.

**Veniti Inc.**, St. Louis, Mo.
Business: Cardiovascular
Date completed: 2015-03-10
Type: Venture financing
Raised: $17 million
Investors: Baird Capital; Tekla Healthcare; Tekla Life Science Investors; Life Sciences Alternative Funding; existing investors
Note: The financing was an undisclosed combination of senior secured debt and equity. The debt was raised from Life Sciences Alternative Funding.

**FINANCIAL NEWS**

**PROPOSED OFFERINGS**

**Aduro Biotech Inc.**, Berkeley, Calif.
Business: Cancer
Date announced: 2015-03-11
Type: IPO
To be raised: Up to $86.3 million
Shares: TBD
Price: TBD
Underwriters: BofA Merrill Lynch; Leerink Partners; William Blair; Canaccord
Note: Aduro is seeking to list its shares on NASDAQ.

**Allergy Therapeutics plc** (LSE:AGY), London, U.K.
Business: Inflammation
Date announced: 2015-03-10
Type: Placing
To be raised: Up to £20.8 million ($31.5 million)
Shares: 94.1 million
Price: 22.1p
Shares outstanding prior: 410.1 million
Placement agent: Panmure

**KemPharm Inc.**, Coralville, Iowa
Business: Neurology
Date announced: 2015-03-11
Type: IPO
To be raised: Up to $57.5 million
Shares: TBD
Price: TBD
Underwriters: Cowen; RBC Capital Markets; Canaccord; Oppenheimer
Overallotment: TBD
Note: KemPharm is seeking to list its shares on NASDAQ.

**Nordic Nanovector A/S**, Oslo, Norway
Business: Cancer
Date announced: 2015-03-11
Type: IPO
To be raised: About NOK400 million ($50.4 million)
Shares: TBD
Price: NOK27-NOK33
Note: Nordic Nanovector is seeking to list its shares on the Oslo Stock Exchange.

**SanBio Co. Ltd.**, Tokyo, Japan
Business: Neurology, Autoimmune, Gene/Cell therapy
Date announced: 2015-03-05
Type: IPO
To be raised: TBD
Shares: 4 million
Price: TBD
Underwriters: Nomura; Mizuho; SBI Securities; SMBC Nikko Capital Markets
Note: SanBio proposed to list its shares on the Tokyo Stock Exchange’s Mothers.
Trillium Therapeutics Inc. (TSX:TR; NASDAQ:TRIL), Toronto, Ontario
Business: Autoimmune, Infectious, Transplant
Date announced: 2015-03-11
Type: Follow-on
To be raised: Up to $57.5 million
Shares: TBD
Price prior: $15.90
Underwriters: Leerink Partners; Cowen

Valeant Pharmaceuticals International Inc. (TSX:VRX; NYSE:VRX), Laval, Quebec
Business: Neurology, Dermatology
Date announced: 2015-03-09
Type: Private placement of senior notes
To be raised: Up to $10.1 billion
Shares: TBD
Price prior: $204.69
Shares outstanding prior: 336.2 million
Note: The offering comprises $2 billion of 5.375% unsecured notes due 2020; $3.3 billion of 5.875% unsecured notes due 2023; €1.5 billion ($1.6 billion) of 4.5% unsecured notes due 2023; and $3.3 billion of 6.125% unsecured notes due 2025. Valeant plans to use the proceeds to fund the acquisition of Salix Pharmaceuticals Ltd. (NASDAQ:SLXP, Raleigh, N.C.). The offering is expected to close on or about March 27. If the Salix deal is not consummated on or prior to Aug. 20, Valeant will be required to redeem the notes at 100% of the issue price, plus accrued and unpaid interest.

FINANCIAL NEWS
WITHDRAWN OFFERINGS

AltheaDx Inc., San Diego, Calif.
Business: Diagnostic, Supply/Service
Date announced: 2015-03-09
Type: IPO
Underwriters: Citigroup; Jefferies; William Blair; Cantor Fitzgerald
Note: AltheaDx withdrew its IPO on NASDAQ, citing market conditions.

Celsius Therapeutics plc (NASDAQ:CLTX), London, U.K.
Business: Inflammation, Dermatology
Date announced: 2015-03-11
Type: Follow-on
Underwriters: Cowen; Piper Jaffray; MTS Securities
Note: Celsius withdrew its offering. The company filed to raise up to $46 million last November.

FINANCIAL NEWS
AMENDED OFFERINGS

Collectis S.A. (Euronext:ALCLS), Paris, France
Business: Gene/Cell therapy, Genomics
Date announced: 2015-03-10
Type: Follow-on
To be raised: TBD
Price prior: €12.53
Underwriters: BoA Merrill Lynch; Piper Jaffray; Jefferies; Oppenheimer; Trout Capital
Note: Collectis amended its offering and removed the amount to be raised. Last month, the company amended the offering to raise up to $115 million and list its ADSs on NASDAQ. Each ADS represents one share.

Orphan Synergy Europe-Pharma S.A., Paris, France
Business: Cancer, Pulmonary
Date announced: 2015-03-09
Type: IPO
To be raised: €18.4 million ($19.9 million)
Shares: 1.7 million
Price: €8-€10.80
Overallotment: 293,250
Note: OSE Pharma amended its IPO and now plans to sell 1.7 million shares at €8 - €10.80. The company said the number of shares in the offering may be increased by up to 250,000 shares via an extension option, which is separate from the overallotment. The offering is expected to close March 24. The company filed its IPO last September.

SteadyMed Ltd., Rehovot, Israel
Business: Drug delivery
Date announced: 2015-03-09
Type: IPO
To be raised: Up to $59.5 million
Shares: 4.3 million
Price: $12-$14
Overallotment: 637,500
Note: SteadyMed amended its IPO on NASDAQ and now plans to sell up to 4.3 million shares at $12-$14. Last month, the company filed to raise up to $55 million.

Valeritas Inc., Bridgewater, N.J.
Business: Drug delivery, Endocrine/Metabolic
Date announced: 2015-03-09
Type: IPO
To be raised: Up to $80 million
Shares: 5 million
Price: $14-$16
Underwriters: Piper Jaffray; Leerink Partners; Oppenheimer
Overallotment: 750,000
Note: Valeritas amended its IPO on NASDAQ and now plans to sell up to 5 million shares at $14-$16. Last month, the company filed to raise up to $90 million.

XBiotech Inc. Austin, Texas
Business: Antibodies
Date announced: 2015-03-10
Type: IPO
To be raised: Up to $80 million
Shares: 4 million
Price: $18-$20
Underwriter: WR Hambrecht
Note: XBiotech amended its IPO and now plans to sell 4 million shares at $18-$20. The offering will be conducted on a best efforts basis. Last month, the company filed to list its shares on NASDAQ.

Note: Eleven Biotherapeutics established an at-the-market program to sell up to $40 million of its common stock. Cowen is the sales agent. The company, which closed Friday at $10.15, has 18.1 million shares outstanding.

Intra-Cellular Therapies Inc. (NASDAQ:ITCI), New York, N.Y.
Business: Neurology
Date announced: 2015-03-11
Note: Intra-Cellular raised $15.9 million through the sale of 661,481 shares at $24 to cover the overallotment from its March 5 follow-on, bringing the total raised to $129.9 million. The company, which closed Friday at $23.48, has 34.9 million shares outstanding.

Tesaro Inc. (NASDAQ:TSRO), Waltham, Mass.
Business: Cancer
Date announced: 2015-03-09
Note: Tesaro raised $18.1 million through the sale of 355,000 shares at $51 to cover the overallotment from its March 3 follow-on, bringing the total raised to $191.5 million. The company, which closed Friday at $58.73, has 39.9 million shares outstanding.

TPG Biologics Inc. Taipei, Taiwan
Business: Antibodies, Supply/Service
Date announced: 2015-03-11
Note: TPG Biologics began the formal process to list on the GreTai Securities Market in Taiwan by applying as an emerging stock on the exchange. The company expects to begin trading as an emerging stock on March 18. To obtain a formal listing on the GreTai exchange, companies must first trade as an emerging stock for at least six months or meet other requirements.

BioLineRx Ltd. (Tel Aviv:BLRX; NASDAQ:BLRX), Jerusalem, Israel
Business: Neurology, Cardiovascular, Infectious
Date announced: 2015-03-11
Note: BioLineRx raised $3.8 million through the sale of 1.9 million ADSs at $2 to cover the overallotment from its March 6 follow-on, bringing the total raised to $28.8 million. The company, which closed Friday at $1.96, has 53.1 million ADSs outstanding. Each ADS represents 10 ordinary shares.

Depomed Inc. (NASDAQ:DEPO), Newark, Calif.
Business: Endocrine/Metabolic, Neurology, Drug delivery
Date announced: 2015-03-12
Note: Depomed secured a $575 million debt facility from Deerfield and Pharmakon. The seven-year loan bears interest at 9.75% plus three-month LIBOR, with a floor of 1% and subject to certain caps, and is secured by Depomed assets. Funding is expected to occur in conjunction with the closing of Depomed’s acquisition of the Nucynta tapentadol analgesic franchise from Johnson & Johnson (NYSE:JNJ, New Brunswick, N.J.), which is slated for next month.

Eleven Biotherapeutics Inc. (NASDAQ:EBIO), Cambridge, Mass.
Business: Ophthalmic
Date announced: 2015-03-11