Breakthrough encore

By Steve Usdin
Washington Editor
Friends of Cancer Research, the advocacy organization that conceived of and persuaded Congress to enact FDA’s breakthrough therapies program, last week unveiled a proposal to expedite development of companion diagnostics that are intended for use with a breakthrough drug.

In contrast to the breakthrough therapies program, which was incorporated into the FDA Safety and Innovation Act, FOCR’s new proposal focuses on steps the agency and diagnostics companies can take to streamline development and review within existing law.

Senior agency officials, including Jeffrey Shuren, director of the Center for Devices and Radiological Health (CDRH), and Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), made it clear they support the proposal in principle at a Sept. 6 meeting sponsored by FOCR.

See next page
Regulation, from previous page

Shuren suggested, however, that supporting the breakthrough diagnostics program may require additional funding.

CDRH wasn’t at the table when the breakthrough therapies program was developed, and the center has not received any additional funds to help it speed the review of breakthrough companion diagnostics applications, he noted.

Shuren said the center has been able to handle the added workload, but “resources are a challenge.” In addition, he said budget sequestration “has thrown a terrible monkey wrench” into CDRH’s finances.

All or most of the breakthrough diagnostics proposals could be implemented without legislation. Many of them echo steps CDRH has already implemented on an informal basis and plans to codify in formal guidance documents, Shuren said.

Rational exuberance

Drug companies, patients and investors have responded enthusiastically to the breakthrough therapies program: as of Aug. 23, CDER had received 82 requests for breakthrough designation. It had granted 25, and 25 were pending.

The program is intended to speed the development of drugs when there is dramatic clinical evidence of efficacy.

The first approval of a breakthrough drug is likely to come this fall, according to FDA officials.

Marketing applications are pending for at least three breakthrough therapies.

Obinutuzumab to treat previously untreated chronic lymphocytic leukemia (CLL), from Roche and its Genentech unit, has a Dec. 20 PDUFA date. Ibrutinib from Pharmacycics Inc. and Johnson & Johnson has a Feb. 28, 2014, PDUFA date for previously treated mantle cell lymphoma (MCL) and previously treated CLL/small lymphocytic lymphoma (SLL).

The PDUFA date is not disclosed for serelaxin from Novartis AG to treat acute heart failure (AHF). In its January earnings announcement, the pharma said it expected a U.S. submission in 2Q13 but it has not disclosed precisely when the application was submitted.

FDA frequently beats PDUFA goals for cancer drugs that, like obinutuzumab and ibrutinib, could provide dramatic improvements over standard care.

The flood of breakthrough designations is a reflection of the progress the biopharma industry has been making in creating targeted therapies, according to Woodcock (see BioCentury, June 24).

At the same time, the rapid development of diagnostics is a prerequisite to speeding the deployment of these breakthrough therapies, said Michael Pacanowski, associate director for genomics and targeted therapy in the Office of Clinical Pharmacology at CDER.

Indeed, about two-thirds of the applications FDA has accepted for its breakthrough therapies program include a companion diagnostic.

Woodcock noted the use of targeting strategies to enhance efficacy in products that have breakthrough designations is not limited to cancer and monogenic hereditary diseases, but also include “other diseases where the biomarkers are more fuzzy.”

Woodcock added that she hopes to see targeting in antibiotic drug development based on improved diagnostic technology.

Despite this central role in targeted medicine, diagnostics were not explicitly included in the breakthrough therapy legislation.

“There is pressing need to clarify the pathways to make both [drugs and companion diagnostics] come to market in a timely fashion,” Pacanowski told the meeting.

In the absence of a process for expediting development of companion diagnostics, “in many cases the co-development of a diagnostic may lag behind” development of a breakthrough therapy, warned Howard Scher, chief of the genitourinary oncology service at Memorial Sloan-Kettering Cancer Center.

See next page
FOCR’s proposal

In an interview on BioCentury This Week television, FOCR Executive Director Jeff Allen said the group and its collaborators has been working to identify “particular strategies for keeping the development time of the diagnostic in line with the compressed development time of an associated breakthrough therapy” (see BioCentury This Week, Sept. 8).

Prior to the advent of breakthrough therapies, FDA stated that it will not allow delays in approving an in vitro diagnostic (IVD) to delay access to an important new drug.

In a 2011 draft guidance on IVD companion diagnostics, the agency said it “may decide to approve a therapeutic product even if its IVD companion diagnostic device is not yet approved or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product with an unapproved or uncleared IVD companion diagnostic device are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device.”

The FOCR proposal, which hasn’t been publicly released, uses this statement as a point of departure for recommendations for streamlining administrative processes, instituting a risk-based review system, and speeding the uptake of newly approved companion diagnostics for breakthrough therapies.

The administrative proposals include automatically assigning Priority Review designation to a breakthrough companion diagnostic and applying the “all hands on deck” approach CDER uses for breakthrough therapies.

Shuren told the meeting that CDRH already assigns companion diagnostics Priority designation, “which means they move to the top of the queue for PMAs.”

He added that CDRH has piloted an “innovation pathway” that provides extensive collaboration and involvement of senior management for breakthrough medical devices.

“It has been successful for the companies; it has helped them reduce the time and cost to come to market. The challenge for us is it is very resource intensive,” Shuren added.

FOCR’s proposal calls for CDRH to use “risk-based processes to determine required analytical studies for each assay type at the time of PMA filing.”

This could involve working with sponsors to determine what data could be supplied postmarket, and in some cases allowing approvals based on premarket submission of data that can be obtained rapidly.

For example, the FOCR proposal suggests that “contrived samples,” such as cell lines, plasmids and serum spiked with recombinant protein could be used instead of actual patient samples for initial assessment of assay performance.

Supplementing patient samples with contrived samples could be particularly helpful for low-prevalence diseases and in instances when specimens are rare.

Tracy Bush, director of companion diagnostic regulatory affairs at Roche, said at the meeting.

The most challenging recommendations — and potentially most consequential — involve streamlining reviews of quality systems.

For example, it might be possible to determine when some quality systems review requirements can be deferred to the postmarket. FOCR’s proposal suggests this approach could be applied “when a device manufacturer is developing an assay for ‘distribution’ to a single lab such as for a rare indication.”

The proposals also suggest FDA could defer some manufacturing process validation to the postmarket, such as for manufacturers that have PMAs for the same or highly similar manufacturing processes.

FOCR also is proposing that CDRH allow sponsors to take steps prior to approval that would speed the deployment of breakthrough companion diagnostics.

“Under current regulations, devices cannot be shipped to laboratories until they are approved and laboratories are verified to perform the testing,” according to the FOCR proposal.

Labs that participated in clinical trials can start offering a companion diagnostic as soon as it is approved, but it can take months for other labs to complete the necessary training, establish standard operating procedures and verify test methods, said Christine Gathers, senior director for regulatory affairs for diagnostics at Eli Lilly and Co.

According to FOCR, CDRH has authority to allow sponsors to ship tests to labs prior to approval, which would allow the labs to set up SOPs and do the necessary training.

Elizabeth Mansfield, director of personalized medicine in CDRH’s Office of In Vitro Diagnostics Device Evaluation and Safety, confirmed FDA could allow such shipments if the labs do not use the tests to report data to physicians.

FDA’s response

“The set of proposals is incredibly on point, incredibly helpful; it echoes a lot of things we have been thinking about internally or have implemented,” Mansfield told the meeting.

She added that the implementation of the specific elements of the risk-based approach “will probably be context dependent,” but the proposals are an “excellent jumping-off point” for internal FDA deliberations.

Shuren said FOCR’s proposal is consistent with CDRH’s goal of having medical devices approved and available to patients in the U.S. before other countries.

He added that CDRH doesn’t have a formal program like CDER’s accelerated approval, but it has implemented an ad hoc process that is intended to accept a greater degree of uncertainty in order to get high priority devices approved more rapidly.

Instead of surrogate endpoints, CDER’s approach involves “shifting requirements from pre- to postmarket,” Shuren said.

The center is working on a formal policy on pre- and postmarket data requirements and “will consider folding the FOCR white paper into the framework.”

CDRH can do a lot to expedite co-development of diagnostics under its existing authority, Shuren said, but he left the door open to asking Congress for additional authority.

“At the present time there is a lot we can do with our current authority. A push from Congress to do things can be helpful, but we are looking at how far we can take this with our current authority and whether we can take it further with an extension of the law.”

See next page
Woodcock stressed the importance of close collaboration between CDER and CDRH, and argued that regulators and sponsors need to change their approach to facilitate breakthroughs. Reviewers and companies need to understand that breakthrough products are a “very different game,” she said, in which “patients are willing to accept much more risk” and are telling regulators “don’t dot all the Is and cross all the Ts, get the products out to us.”

But as the agency starts to approve breakthrough therapies based on less data than is traditionally available, attention will shift to coverage and reimbursement of drugs and companion diagnostics — topics that are not addressed by FOCR’s proposals.

On reimbursement in particular, the value of innovator diagnostics has yet to be hashed out with Medicare and private payers.

Speaking on BioCentury This Week television, Robert McCormack, head of Technology Innovation at Janssen Diagnostics, and Kate Claessens, senior director of health policy and reimbursement at Roche Diagnostics, argued that reimbursement should be tied to evidence of clinical utility — that the use of the diagnostic actually can be shown to improve patient outcomes.

“I think the price a test receives should be incumbent upon the evidence behind it,” said McCormack.

COMPANIES AND INSTITUTIONS MENTIONED

- Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
- Friends of Cancer Research (FOCR), Washington, D.C.
- Genentech Inc., South San Francisco, Calif.
- Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
- Memorial Sloan-Kettering Cancer Center, New York, N.Y.
- Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
- Pharmacyclics Inc. (NASDAQ:PCYC), Sunnyvale, Calif.
- Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
- U.S. Food and Drug Administration (FDA), Silver Spring, Md.
Strategy

Setting Amgen’s targets

By Erin McCallister
Senior Writer

Amgen Inc.’s proposed acquisition of Onyx Pharmaceuticals Inc. will more than double the bellwether’s portfolio of marketed targeted cancer therapeutics, putting it in a tie with GlaxoSmithKline plc for second place behind Roche and its Genentech Inc. unit. The question is what Amgen’s next act will be.

After two months of negotiations, Amgen agreed in August to purchase Onyx for $10.4 billion (see BioCentury, Sept. 2).

The deal will increase Amgen’s portfolio of marketed cancer drugs to five from two through the addition of Nexavar sorafenib, Stivarga regorafenib and Kyprolis carfilzomib.

Onyx also adds one Phase II cancer compound to Amgen’s five Phase II or III programs, excluding line extensions and compounds for which worldwide rights have been out-licensed.

Targeted cancer therapy leaders Roche and Genentech have eight targeted drugs marketed across 20 indications, plus 10 targeted programs in Phase II or beyond.

Amgen is now even with GlaxoSmithKline’s five marketed targeted drugs. The biotech now tops Bristol-Myers Squibb Co. and Pfizer Inc., which have three apiece, and Novartis AG, which has four. All four pharmas have Phase II and Phase III pipelines that are about as robust as Amgen’s.

Part of Amgen’s plan for continuing to climb the ladder will be to expand the label for Kyprolis — the real driver behind last month’s deal.

That strategy is similar to what Amgen did with Xgeva denosumab, which was first approved to prevent skeletal-related events (SREs) in metastatic disease and then was expanded to treat giant cell tumor of the bone.

Both Xgeva and Kyprolis were designed to unseat established drugs whose efficacy, while not perfect, was both clearly demonstrated and well understood by physicians.

A difference, however, is that Xgeva is a first-in-class human mAb targeting receptor activator of NF-kappa B ligand (RANKL). It was approved based on head-to-head data from three Phase III trials against the standard of care.

In contrast, Kyprolis belongs to the same proteasome inhibitor class as Velcade bortezomib, which is SOC — and the newcomer received accelerated approval based on a surrogate endpoint in a single-arm Phase II study.

To grow Kyprolis, Amgen will need to confirm the drug’s benefit on a clinical endpoint, complete two ongoing head-to-head studies against Velcade to help move Kyprolis up in the MM treatment armamentarium and potentially explore additional indications.

Data from the confirmatory ASPIRE trial, as well as results from the FOCUS trial to support European approval, are due in 1H14.

“Kyprolis is at an early stage in its lifecycle, and that’s important to us as we feel that this is a point where we can still help maximize the full potential of the product.”

Robert Bradway, Amgen

Next up from Amgen’s internal pipeline is the oncolytic virus Talimogene laherparepvec, which will have overall survival (OS) data in melanoma this year.

Bulking up

While Amgen built a name for itself among oncologists with supportive care blockbusters Aranesp darbepoetin alfa, Epogen epoetin alfa, Neupogen filgrastim and Neulasta pegfilgrastim, it has only two direct cancer treatments: Xgeva and colorectal cancer drug Vectibix panitumumab.

Onyx adds two drugs partnered with Bayer AG, and Kyprolis, to which the biotech has full rights.

Nexavar is approved in more than 100 countries to treat hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC). Onyx markets Nexavar with Bayer in the U.S. and shares equally in the drug’s profits and losses worldwide, except in Japan, where Bayer has rights.

Onyx co-promotes Stivarga with Bayer for metastatic colorectal cancer (mCRC) and gastrointestinal stromal tumor (GIST) in the U.S. Last month, Stivarga was approved in the EU to treat mCRC.

For 1H13, Onyx recorded $19.3 million in royalty revenues for Stivarga and revenues of $152 million for Nexavar.

The centerpiece of the deal, Kyprolis, received accelerated approval in July 2012 to treat MM in patients who have progressed after treatment with at least two prior therapies including an immunomodulator and Velcade.

On June 30, Kyprolis generated six-month worldwide net sales of $125 million. The drug posted $64 million in sales in 2012.

“Kyprolis is at an early stage in its lifecycle, and that’s important to us as we feel that this is a point where we can still help maximize the full potential of the product by virtue of our experience with Xgeva, which has been one of the most successful oncology launches in the past five years,” said Amgen Chairman and CEO Robert Bradway on a call with investors.

The company declined BioCentury’s request for an interview.

Xgeva was first approved in the U.S. in 2010 to prevent SREs in patients with bone metastases from solid tumors.

This June, FDA approved Xgeva to treat giant cell tumor of the bone, an Orphan indication.

Xgeva sales were $8 million in 2010, $351 million in 2011, $748 million in 2012 and $472 million in 1H13.

Upward climb

Amgen hopes Kyprolis will follow a similar trajectory. However, the markets for each drug and the amount of evidence available at launch are very different.
Xgeva was designed to be safer and more effective than Novartis’ Zometa zoledronic acid, which was SOC to prevent bone metastases in cancer patients. Zometa acts later in the pathway than Xgeva, after the formation of osteoclasts, making it more likely that some tumor cells could attach before the osteoclasts are destroyed. Xgeva prevents osteoclasts from forming.

Amgen also expected Xgeva’s specificity and reversibility to result in less renal toxicity and fewer acute phase reactions compared with Zometa.

The BLA for Xgeva included data from three trials of Xgeva in over 5,000 patients with advanced breast and prostate cancer as well as other solid tumors. All three trials met the non-inferiority endpoint vs. Zometa on time to SRE. In the breast and prostate trials, Xgeva was superior to Zometa.

Xgeva did not have the renal toxicity or acute phase reactions seen with Zometa.

Kyprolis also was developed to provide both an efficacy and safety advantage over SOC, which in newly diagnosed MM patients who had received at least two prior therapies. The ORR for Velcade was 27.7%

In 2005, the drug received full approval for MM patients who had received at least one prior therapy based on a randomized Phase III trial vs. high-dose dexamethasone in relapsed MM following one to three prior therapies. Velcade met the primary endpoint of time to progression with a median TTP of 6.4 months vs. 3.5 months for the control group (p<0.0001).

In 2008, FDA approved Johnson & Johnson’s (AMGN) Kyprolis for treatment of first-line MM. Approval of subcutaneous dosing followed in January 2012.

Revlimid is a thalidomide analog that was approved for MM in 2006 for patients who had received at least one prior therapy.

The drug was approved based on two Phase III studies in MM patients with at least one prior therapy. The Revlimid groups in two Phase III trials had ORRs of 61% and 59% vs. 19% and 23% for the dexamethasone groups. Velcade was not used in these trials.

Kyprolis does appear to have a tolerability advantage over Velcade. In the Kyprolis trials, patients on the drug had fewer cases of grade 3-4 neutropenia and thrombocytopenia vs. Velcade. Kyprolis also was developed to provide both an efficacy and safety advantage over SOC, which in newly diagnosed MM patients who had received at least two prior therapies. The ORR for Velcade was 27.7%

In 2005, the drug received full approval for MM patients who had received at least one prior therapy based on a randomized Phase III trial vs. high-dose dexamethasone in relapsed MM following one to three prior therapies. Velcade met the primary endpoint of time to progression with a median TTP of 6.4 months vs. 3.5 months for the control group (p<0.0001).

In 2008, FDA approved Johnson & Johnson’s (AMGN) Kyprolis for treatment of first-line MM. Approval of subcutaneous dosing followed in January 2012.

Revlimid is a thalidomide analog that was approved for MM in 2006 for patients who had received at least one prior therapy.

The drug was approved based on two Phase III studies in MM patients with at least one prior therapy. The Revlimid groups in two Phase III trials had ORRs of 61% and 59% vs. 19% and 23% for the dexamethasone groups. Velcade was not used in these trials.

Kyprolis does appear to have a tolerability advantage over Velcade. In the Kyprolis trials, patients on the drug had fewer cases of grade 3-4 neutropenia and thrombocytopenia vs. Velcade.

What’s next from Amgen’s cancer pipeline

Following its acquisition of Onyx Pharmaceuticals Inc. (NASDAQ:ONXX), Amgen Inc. (NASDAQ:AMGN) will have at least six targeted cancer therapies in Phase II and Phase III, excluding line extensions and compounds to which worldwide rights have been out-licensed. The next readouts from Amgen’s Phase III internal programs will come this year with survival data for Talmogene laherparepvec (formerly OncoVEX) in melanoma followed by data for trebananib (AMG 386) in ovarian cancer in 2014. Source: BCIQ: BioCentury Online Intelligence; company documents; www.clinicaltrials.gov

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Indication</th>
<th>Status [milestone]</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talamogene laherparepvec</td>
<td>Modified herpes simplex virus type 1 (HSV-1) encoding GM-CSF</td>
<td>Melanoma</td>
<td>Ph III [overall survival data by YE'13]</td>
<td>From 2011 acquisition of BioVex Inc.</td>
</tr>
<tr>
<td>Trebananib (AMG 386)</td>
<td>Recombinant Fc-peptide fusion protein (peptibody) targeting angiopoietins</td>
<td>Ovarian cancer</td>
<td>Ph III (ovarian) [data in 2014]; Ph II (other cancers)</td>
<td>Takeda Pharmaceutical Co. Ltd. (Tokyo:4502) has Japanese rights</td>
</tr>
<tr>
<td>Rilotumumab (AMG 102)</td>
<td>Human mAb against human hepatocyte growth factor/scatter factor (HGF/SF)</td>
<td>Gastric cancer</td>
<td>Ph III [final data collection for primary endpoint in Dec 2015]</td>
<td>NA</td>
</tr>
<tr>
<td>Blinatumomab (AMG 103)</td>
<td>Bispecific T cell engager (BiTE) against CD19</td>
<td>Acute lymphoblastic leukemia (ALL); non-Hodgkin’s lymphoma (NHL)</td>
<td>Ph II [multiple trials with final data collection for primary endpoints over 2013-14]</td>
<td>From 2012 acquisition of Micromet Inc.</td>
</tr>
<tr>
<td>AMG 888 (U3-1287)</td>
<td>Human mAb against EGFR 3 (HER3; ErbB3)</td>
<td>Breast cancer; non-small cell lung cancer (NSCLC)</td>
<td>Ph I/II [final data collection for primary endpoint in metastatic breast cancer trial in Dec 2013]</td>
<td>Co-developing with Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568)</td>
</tr>
<tr>
<td>Oprozomib</td>
<td>Oral proteasome inhibitor</td>
<td>Multiple myeloma (MM)</td>
<td>Ph I/II [multiple trials with final data collection for primary endpoints ranging from 2014-2016]</td>
<td>From Onyx; Ono Pharmaceutical Co. Ltd. (Tokyo:4528; Osaka:4528) has Japanese rights</td>
</tr>
</tbody>
</table>
of peripheral neuropathy, with 14% of patients reporting the side effect. Only 1% of patients experienced grade 3 peripheral neuropathy and <1% experienced more severe cases.

In the pivotal trial that supported initial approval of Velcade, peripheral neuropathy was reported in 37% of patients, including 14% with grade 3 events.

Subcutaneous dosing of Velcade reduces peripheral neuropathy, but the rates are still higher than those for Kyprolis.

In a Phase III open-label, non-inferiority study in 222 patients with relapsed MM, the rates of grade 2 and higher peripheral neuropathy were 24% in the subcutaneous Velcade group and 39% in the IV group. Subcutaneous Velcade was associated with grade 3 or higher peripheral neuropathy in 6% of patients vs. 15% for the IV group.

Revl imid has peripheral neuropathy rates that are similar to those for Kyprolis.

To support approval of Kyprolis in the EU, Onyx is running the Phase III FOCUS trial, which is evaluating Kyprolis as a single agent vs. best supportive care in patients who have received at least three prior therapies. The primary endpoint is OS.

Onyx also has three ongoing trials that aim to move Kyprolis earlier in MM treatment, one in combination with Revlimid, and two going head-to-head against Velcade.

ASPIRE is the confirmatory trial required by FDA. The Phase III study is evaluating Kyprolis plus Revlimid and dexamethasone in patients with relapsed MM who have received one to three prior therapies. The primary endpoint is progression-free survival (PFS), with an interim analysis expected in 1H14.

Amen would not disclose when data from the head-to-head ENDEAVOR and CLARION trials in newly diagnosed MM are expected. According to clinicaltrials.gov, the estimated primary completion date is January 2015 for ENDEAVOR and April 2016 for CLARION. The endpoint in both is PFS.

Kyprolis is also being tested in investigator-led studies beyond MM, including a Phase I study by MD Anderson Cancer Center in lymphoma patients after stem cell therapy; a Phase I study by Washington University School of Medicine in relapsed acute myeloid and acute lymphoblastic leukemia (AML and ALL); and a Phase II/III study by MD Anderson in relapsed/refractory mantle cell lymphoma.

According to clinicaltrials.gov, results from the leukemia study are expected next month, followed by the lymphoma study in 2016 and the mantle cell lymphoma study in 2018.

Behind Kyprolis

On Amgen’s conference call, Bradway noted the company already has begun to build a relationship with the MM community through a Phase III trial of Xgeva to prevent SREs in these patients.

“This is a community that we are directly involved in and [we are] excited to have the potential to talk to them about a therapy that makes a real difference for their patients,” he said.

The primary endpoint in the MM trial of Xgeva is time to the first on-study SRE. Data are expected in 2018.

Amgen also has a pipeline of cancer programs that target multiple cancer pathways, including tumor angiogenesis, growth regulation, and hematopoiesis, as well as oncolytic immunotherapy.

The biotech has four internal programs in Phase III, two of which could be first in class. Talimogene (formerly OncoVEX) is a modified herpes simplex virus type 1 (HSV-1) encoding GM-CSF. The program, which Amgen gained from its 2011 acquisition of BioVex Inc., is in Phase III testing for melanoma (see BioCentury, Jan. 31, 2011).

In March, Amgen reported top-line data showing Talimogene met the primary endpoint of improving durable response rate (16% vs. 2% for control, p<0.0001).

The second program with first-in-class potential is trebananib, a recombinant Fc-peptide fusion protein (peptibody) targeting angiopoietin 1 (ANG1; ANGPT1) and ANG2 that is in separate Phase III trials for ovarian and peritoneal cancers. Data for the ovarian cancer trial are expected next year (see “What’s Next from Amgen’s Cancer Pipeline,”A6).

Amgen also has Phase II trials of trebananib in breast, colorectal, liver and non-small cell lung cancers (NSCLC).

Onyx has one clinical program. Oprozomib, an oral proteasome inhibitor, is in Phase Ib/II testing for MM.

Onyx also is eligible for 8% royalties on sales of palbociclib by Pfizer. The oral small molecule cyclin dependent kinase 4 (CDK4) and CDK6 inhibitor is in Phase III testing for ER+/HER2-advanced breast cancer and has breakthrough designation from FDA.

Amgen hasn’t said whether it will continue to look for late-stage oncology assets, but the company has been active in acquiring or licensing new oncology programs.

In addition to the 2011 acquisition of BioVex, Amgen acquired Micromet Inc. in January 2012 for $1.2 billion (see BioCentury, Jan. 30, 2012).

Amgen gained Micromet’s bispecific T cell engager (BiTE) technology. A BiTE against CD19 is in Phase II testing for ALL. When Amgen did the deal, the company said it would look to expand the BiTE technology to solid tumors.
**Product Discovery & Development**

**Checkpoint complementarity**

By Emily Cukier-Meisner
Senior Writer

The acquisition of Amplimmune Inc. adds a new set of immune checkpoint targets to MedImmune LLC’s cancer portfolio, giving it more potential combinations to test in cancer.

The AstraZeneca plc unit now has four disclosed checkpoint inhibitors addressing four different targets. Although the programs are much earlier stage, that’s the same number disclosed by Bristol-Myers Squibb Co., whose melanoma drug Yervoy ipilimumab was the first checkpoint inhibitor to reach the market (see “Dueling Checkpoint Pipelines”).

Checkpoint proteins are regulatory components of the immune system that can act as immune activators or suppressors to prolong or prevent an immune response.

Under the late August deal, MedImmune will pay $225 million up front and up to $275 million in development milestones. The deal includes a portfolio of preclinical immune checkpoint modulators, but the only specific program that was disclosed is AMP-514, a blocker of the PD-1 receptor (PDCD1; PD-1; CD279).

Amplimmune’s investors did well. The company, which was founded in 2007, did a single venture round, raising $20 million in a series A that year from InterWest Partners and the Wellcome Trust.

InterWest and Wellcome are already getting more than a 10x return, which could increase to 25x if all the milestones are met.

MedImmune and Amplimmune began with partnering discussions, but Amplimmune SVP and COO Gary Fanger said talks shifted toward acquisition in late spring, particularly after data presented by companies such as Bristol-Myers Squibb Co. and

---

### Dueling checkpoint pipelines

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Indication</th>
<th>Status</th>
<th>Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>MedImmune LLC/AstraZeneca plc (LSE:AZN; NYSE:AZN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremelimumab (CP-675; CP-675,206; CP-675,5206)</td>
<td>Human mAb against CTLA-4 receptor (CD152)</td>
<td>Solid tumors</td>
<td>Ph II</td>
<td>Pfizer Inc. (NYSE:PFE)</td>
</tr>
<tr>
<td>MEDI4736</td>
<td>Human mAb targeting programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1)</td>
<td>Solid tumors</td>
<td>Ph I</td>
<td></td>
</tr>
<tr>
<td>MEDH469 (anti-OX40)</td>
<td>Murine mAb agonist of tumor necrosis factor (TNF) receptor superfamily member 4 (TNFRSF4; OX40; CD134)</td>
<td>Solid tumors</td>
<td>Ph I</td>
<td>AgonOx</td>
</tr>
<tr>
<td>AMP-514</td>
<td>mAb against PD-1 receptor</td>
<td>Cancer</td>
<td>Preclin</td>
<td></td>
</tr>
<tr>
<td>Bristol-Myers Squibb Co. (NYSE:BMY)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yervoy ipilimumab</td>
<td>Human mAb against CTLA-4</td>
<td>Melanoma; lung cancer; prostate cancer; gastric cancer; other cancers</td>
<td>Mkt (melanoma); Ph I-Ph III (melanoma and other cancers)</td>
<td>Ono Pharmaceutical Co. Ltd (Tokyo:4528; Osaka:4528)</td>
</tr>
<tr>
<td>Nivolumab (BMS-936558; MDX-1106; ONO-4538)</td>
<td>Human mAb against PD-1 receptor (PDCD1; PD-1; CD279)</td>
<td>Melanoma; non-small cell lung cancer (NSCLC); renal cancer; solid tumors; hematologic malignancies</td>
<td>Ph III (melanoma, NSCLC, renal); Ph I-Ph II (solid tumors, hematologic)</td>
<td></td>
</tr>
<tr>
<td>Urelumab (BMS-663513)</td>
<td>Human mAb agonist of tumor necrosis factor (TNF) receptor superfamily member 9 (TNFRSF9; 4-1BB, CD137)</td>
<td>Cancer</td>
<td>Ph I</td>
<td></td>
</tr>
<tr>
<td>Anti-LAG3</td>
<td>mAb against lymphocyte-activation gene 3 (LAG3; CD223)</td>
<td>Cancer</td>
<td>Preclin</td>
<td></td>
</tr>
</tbody>
</table>

SciBX This Week

ANALYSIS

COVER STORY

Post-translational mAbs
UCSF researchers have developed a platform capable of producing mAbs that target post-translational modifications such as phosphorylation. The technology could open up a host of new targets for cancer and other diseases associated with aberrant modifications. Next, the team will have to show that the mAbs target endogenous proteins in vivo.

TARGETS & MECHANISMS

IncRNA meets the androgen receptor
The identification of two long noncoding RNAs that act directly on the androgen receptor and are required for castration-resistant prostate cancer growth provide new targets for the disease. The results also illustrate a previously unknown mechanism of action for IncRNAs.

Ex-SASP-erating cancer
German researchers have identified a hypermetabolic phenotype in senescent tumor cells that exerts tumorigenic effects on other cells in the tumor microenvironment. Although small molecule inhibitors of the phenotype improved survival in a mouse model of lymphoma, future studies will need to determine whether the phenotype occurs in primary tumors.

Epilepsy narrows down
A spate of human genetic studies has identified mutations in NMDAR subunits as a root cause of idiopathic focal epilepsy, a common childhood form of the disease. The studies suggest that a group of epilepsies and encephalopathies marked by seizures, aphasia and learning disorders could be treated with NMDAR-selective modulators.

THE DISTILLERY

This week in therapeutics
Improving the tolerability of chemoradiotherapy with RSPO1 and SLIT2; treating heart failure with BET bromodomain inhibitors; preventing graft-versus-host disease through PRKCA and PRKCQ inhibition; and more...

This week in techniques
Biosynthesis of GE2270 and derivatives in Nonomuraea; a mouse model of atopic dermatitis–like inflammation; 2’-O-methyltransferase–deficient, live, attenuated dengue virus vaccine; and more...

FROM THE MAKERS OF BioCentury and nature
Request a Free Trial
scibx@biocentury.com

Product Discovery & Development,
from previous page

Merck & Co. Inc. at the American Society of Clinical Oncology meeting highlighted mid-stage cancer immunotherapeutics.

At ASCO, updated Phase Ib data on BMS's nivolumab showed one-year overall survival (OS) rates of 42-70% and two-year survival rates of 14-50% across advanced melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC).

BMS also presented the first clinical data on a checkpoint modulator combination: Yervoy plus nivolumab in metastatic melanoma. All 17 patients receiving 1 mg/kg nivolumab and 3 mg/kg Yervoy — the most effective of four doses tested — showed at least 80% tumor shrinkage within 12 weeks.

By comparison, Yervoy showed similar shrinkage in fewer than 2% of patients in its Phase III trial. Nivolumab monotherapy produced that kind of shrinkage in fewer than 3% of patients in its Phase Ib trial (see BioCentury, June 10).

Yervoy targets CTLA-4 (CD152). Like AMP-514, nivolumab targets PD-1.

Edward Bradley, SVP and head of innovative medicines in oncology at MedImmune, told BioCentury that AMP-514 has differences compared to other anti-PD-1 mAbs, both in downstream effects and in activity in preclinical models. He believes these could translate into different antitumor activity in the clinic.

Bradley added Amplimmune’s portfolio is particularly strong in B7 proteins, a family of immune checkpoint targets that modulate signaling between antigen-presenting cells (APCs) and T cells.

At least six B7 family members were discovered in the labs of Amplimmune co-founders Lieping Chen and Drew Pardoll, including programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1), programmed cell death 1 ligand 2 (PDCD1LG2; B7-DC; PD-L2), B7-H3 (CD276) and B7-H4 (V-set domain containing T cell activation inhibitor; VTCN1).

Chen is professor of immunobiology, dermatology and medicine and director of cancer immunology at the Yale University School of Medicine. Pardoll is professor of oncology, medicine, pathology, and molecular biology and genetics and co-director of the division of immunology and hematology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University.

“Amplimmune has some novel and proprietary technology that is useful in assessing biologically relevant immune activity of their various antibodies,” Bradley noted.

“It wouldn’t have made sense to just go after an asset when in fact the value really is in the total package — it’s in all of the assets that they have, plus the people, plus the synergy of that group with the scientists that we have here,” he said.

Indeed, Amplimmune President and CEO Michael Richman and SVP and CSO Sol Langermann have worked at MedImmune. Richman was SVP of corporate development, and Langermann held multiple positions including senior director in the department of cell biology.

Amplimmune plans to submit an IND for AMP-514 in October and start clinical trials no later than 1Q14. Bradley anticipates moving additional Amplimmune compounds into the clinic within a year.

See next page
Combining checkpoints

Part of what makes a bigger portfolio of checkpoint modulators attractive is the potential for combining different immune checkpoint mechanisms.

Tumors can hijack these regulatory systems to evade the antitumor immune response. Checkpoint modulators therefore seek to resensitize tumors to the immune response by shutting down negative immune regulators or boosting stimulatory molecules.

Before the acquisition, MedImmune already planned to explore combinations of its three other disclosed checkpoint modulators. Specifically, the company planned to test two combinations involving its anti-CTLA-4 mAb tremelimumab: one with MEDI6469, a mAb agonist of tumor necrosis factor (TNF) receptor superfamily member 4 (TNFRSF4; OX40; CD134), and another with MEDI4736, a mAb against PD-L1.

Tremelimumab is in Phase II testing to treat unresectable malignant mesothelioma. MedImmune in-licensed the mAb from Pfizer Inc., which retains rights for undisclosed combination therapies.

MEDI6469 is in Phase I to treat cancer. It was developed using OX40 agonist technology from AgonOx.

MEDI4736 is in Phase I to treat cancer. Bradley would not say what additional combinations MedImmune plans to explore. But he noted that combining targeted therapies against PD-1 and PD-L1 could be interesting because it might block the entire PD-1 pathway.

He added that clinical studies of PD-1 and PD-L1 monotherapies have shown each target has additional biologic activities outside of the receptor/ligand interaction.

MedImmune plans to use undisclosed preclinical technology from Amplimmune alongside its own preclinical capabilities and animal models to assess immune activity of combinations. It will conduct small clinical trials of the combinations and use pharmacodynamic markers to confirm activity before moving to larger trials.

MedImmune also will assume Amplimmune’s rights and obligations for two partnered compounds.

Under a 2010 deal, GlaxoSmithKline plc has an exclusive worldwide license to AMP-224, a fusion protein that blocks the interaction between PD-1 and PD-L1. AMP-224 is in Phase I in patients with advanced cancer.

In January, Amplimmune granted Daiichi Sankyo Co. Ltd. an exclusive option to AMP-110, a fusion protein containing the extracellular domain of B7-H4 and the Fc-portion of IgG. AMP-110 is in Phase I testing to treat patients with rheumatoid arthritis (RA).

Amplimmune is responsible for manufacturing and development through a Phase II POC trial.

MedImmune also will keep all of Amplimmune’s employees, and the company will become a subsidiary of MedImmune.

Fanger expects the acquisition to close at the beginning of 4Q.

**COMPANIES AND INSTITUTIONS MENTIONED**

- AgonOx, Portland, Ore.
- American Society of Clinical Oncology (ASCO), Arlington, Va.
- Amplimmune Inc., Gaithersburg, Md.
- AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
- Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
- Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568), Tokyo, Japan
- GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
- Johns Hopkins University, Baltimore, Md.
- MedImmune LLC, Gaithersburg, Md.
- Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
- Pfizer Inc. (NYSE:PFE), New York, N.Y.
- Yale University School of Medicine, New Haven, Conn.
**Product Discovery & Development**

**Viral persistence**

By Michael Flanagan  
Senior Writer

Theraclone Sciences Inc. was to present data Sept. 8 showing TCN-032 missed the primary endpoint in a Phase IIa influenza viral challenge study. However, the company says the endpoint, rather than the mAb, was the problem.

Based on a trend of symptomatic improvement and significant improvements on secondary endpoints including viral shedding and clinical measures, Theracloon hopes to get a government contract to fund the rest of the Phase II program, with an initial focus on seriously ill hospitalized flu patients.

**“We saw a decline in both shedding and symptoms score, which are in line with one another.”**

Eleanor Ramos, Theraclone

TCN-032 is a human mAb against a highly conserved epitope on the amino-terminal extracellular domain (M2e) of the influenza A virus matrix protein. The M2e epitope codes for an ion channel that is essential to the virus’ ability to infect cells. TCH-032 targets a five amino-acid sequence on M2e present in every strain of influenza studied to date.

The compound is a non-neutralizing antibody that binds either infected cells or free virus “and lets the immune system come in and wallop the immune complex or virus so that it doesn’t have a chance to mutate and develop resistance,” said CEO Clifford Stocks.

Because the antibody recruits immune cells but doesn’t kill the virus, Theracloon did not expect to see a quick result on viral shedding, the endpoint used in viral challenge studies of neuraminidase inhibitors.

Instead, the Phase IIa trial measured the proportion of subjects with grade two or higher influenza symptoms or fever as the primary endpoint. The endpoint included 10 flu-related symptoms — such as cough, headache and fever — that patients were asked to record in a diary for a week.

**ROI are trademarks of BioCentury Publications, Inc. All rights reserved.**

The trial did meet several secondary endpoints, including — unexpectedly — reducing viral shedding from the nasal mucosa by 2.2 log10 compared to placebo (p=0.095, with p>0.10 being the threshold for significance).

On the secondary endpoint of total symptom score, TCN-032 achieved a statistically significant 35% reduction vs. placebo (p=0.0466).

On time to resolution of influenza symptoms, another secondary endpoint, TCN-032 resulted in a non-significant reduction of one day compared to placebo (p=0.06).

“The nice thing is that we saw a decline in both shedding and symptoms score, which are in line with one another,” Ramos said.

The next study will be a Phase II trial in hospitalized patients that will begin in IH14. The primary endpoint will be safety.

Having come full circle on endpoints, Theracloon plans to use viral shedding as the “main” efficacy endpoint “because that is more quantitative and can help us determine a dose,” Ramos said.

Other efficacy endpoints will include time on ventilator and length of stay in the ICU and hospital, according to Stocks.

“The pharmacoeconomics of the hos-
pital setting are such that it would be beneficial to keep these folks out of ICU, off ventilators and shorten their duration of stay by getting them well faster," he said.

The study will evaluate TCN-032 in combination with Tamiflu oseltamivir. Roche markets the neuraminidase inhibitor under a license from Gilead Sciences Inc.

Ramos said Tamiflu was approved based on time to symptom resolution, which she expects will be the endpoint in Phase III trials of TNC-032.

To fund the Phase II study, Theraclone is seeking a $30-$35 million contract from HHS’s Biomedical Advanced Research and Development Authority (BARDA). Theraclone submitted a proposal to BARDA late last month and expects a decision within the next four months.

Theraclone will have help with that process from biodefense play PharmAthene Inc., with which it is merging.

PharmAthene has been awarded more than $550 million in government contracts and funding to support development of a pair of anthrax products and a nerve agent poisoning program.

Theraclone will own 50% of the surviving entity, which will retain the PharmAthene name. Stocks will become president and CEO, while PharmAthene President and CEO Eric Richman will be a director.

If the contract does not come through, Stocks said the fallback will be to evaluate partnering options, such as out-licensing rights in certain geographies.

He said Korea and China “in particular look interesting” because potentially pandemic strains of flu have been emerging there.

In 2010, Zenyaku Kogyo Co. Ltd. exercised an option to license exclusive Japanese rights for Theraclone’s influenza programs, which include TCN-032.

BioCentury makes people think

We know you have many choices for headlines. But if you need to know what the news means, there is only one journal — BioCentury, the Bernstein Report on BioBusiness™ — that is recognized by key decision makers as the best source of perspective, interpretation and analysis for top managers and investors in the biotech community.
Emerging Company Profile

Ixchelsis: Lasting longer

By Tim Fulmer
Senior Writer

Ixchelsis Ltd.’s oxytocin receptor antagonist could help treat premature ejaculation more safely than antidepressant SSRIs, which are prescribed off label for the condition.

Premature ejaculation is one of the most common male sexual dysfunctions and affects 20-30% of men worldwide. While definitions of the condition vary, there is general agreement that premature ejaculation occurs prior to or very soon after vaginal penetration, with concomitant sexual dissatisfaction and emotional distress.

Besides psychotherapy and behavioral therapy, two classes of drugs have been prescribed — topical local anesthetics such as lidocaine and off-label selective serotonin reuptake inhibitors (SSRIs) such as the antidepressants Paxil paroxetine from GlaxoSmithKline plc and Zoloft sertraline from Pfizer Inc. In the EU, one SSRI is marketed to treat premature ejaculation: Priligy dapoxetine from Furiex Pharmaceuticals Inc. and Johnson & Johnson.

In multiple placebo-controlled trials, SSRIs increased the intravaginal ejaculatory latency time (IELT), a measure of the time elapsed prior to ejaculation. However, SSRIs are associated with side effects including nausea, headache, insomnia, dizziness and, in some cases, psychological impairments like suicidal ideation.

Ixchelsis’ oxytocin receptor (OXTR) antagonist IX-01 is designed to have equal or better efficacy than SSRIs without their side effects.

“Oxytocin signaling is a good target in this indication because it’s a key controller of ejaculation,” CEO Gary Muirhead told BioCentury.

In both men and rodents, increased systemic levels of oxytocin are observed during sexual activity leading up to orgasm, and thus blocking the peptide hormone’s receptor is expected to delay orgasm and potentially treat premature ejaculation, he said.

IX-01 was discovered and developed at Pfizer’s Sandwich, U.K., facility. When the site closed in 2011, Muirhead and Ian Osterloh formed Ixchelsis to develop the compound. The two had been part of the pharma’s research program in men’s sexual health and urology.

Pfizer had run a Phase I trial testing the safety and tolerability of a single ascending dose of IX-01 in healthy volunteers. The compound was well tolerated.

Pfizer had run a Phase I trial testing the safety and tolerability of a single ascending dose of IX-01 in healthy volunteers. The compound showed minimal side effects in those volunteers even at supratherapeutic doses, said Muirhead.

“We anticipate that a key advantage of IX-01 compared with the SSRIs is that it will have a much more benign side effect profile and yet have an efficacy at least equal to, if not better than, those compounds,” he said.

Ixchelsis acquired the rights in exchange for an undisclosed equity stake.

In August, Ixchelsis said it raised $14 million in a series A round from TVM Capital’s TVM Life Science Ventures VII fund. Eli Lilly and Co. is an LP in the fund. The pharma has an option to acquire IX-01 if undisclosed milestones are met.

The round will be used to help support the clinical program of IX-01 over the next three years, said Muirhead.

“Our key priorities now include manufacturing scale-up and dosing formulation, as well as two clinical trials,” he said. “We will run a second Phase I safety trial in healthy volunteers, this time looking at multiple ascending doses. Then we will run a placebo-controlled Phase IIa trial in patients, with the primary endpoint of IELT.”

He declined to provide a specific timeline.

Lilly’s Chorus virtual drug development group will be involved throughout the clinical program, said Muirhead.

GSK’s epelsiban (GSK557296) OXTR antagonist also is in development for premature ejaculation. In August, the pharma published final Phase II data in the Journal of Sexual Medicine showing a single dose of epelsiban one hour before sex missed the primary endpoint of an increase in IELT versus placebo in 77 men with premature ejaculation. The compound was well tolerated.

The status of the compound is unclear. GSK did not respond to requests for comment.

COMPANIES AND INSTITUTIONS MENTIONED

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Furiex Pharmaceuticals Inc. (NASDAQ:FURX), Morrisville, N.C.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Ixchelsis Ltd., Sandwich, U.K.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Pfizer Inc. (PFE), New York, N.Y.

All press releases, news announcements and story inquiries should be submitted to our news room at pressreleases@biocentury.com. Editorial announcements emailed to the Editor-in-Chief and/or the Publisher may not receive immediate attention and potential stories will be delayed.
Better decisions post-Avandia

By Erin McCallister
Senior Writer

Three doctors who sit on FDA’s Endocrinologic and Metabolic Drugs Advisory Committee have asked the agency to ease cardiovascular requirements for diabetes drugs now that it is known that Avandia rosiglitazone from GlaxoSmithKline plc did not pose the CV risk that meta-analysis had suggested it might.

The agency said it is “premature” to discuss its stance on the requirements for CV testing of diabetes drugs. But there are at least two initiatives under way that could help FDA more swiftly address safety questions that arise postmarket.

First, FDA is building its Sentinel system to query electronic patient records to identify and monitor postmarket safety concerns. The agency has already conducted at least two pilot postmarket safety assessments.

Second is FDA’s benefit-risk framework initiative, which includes an effort to develop a consistent approach to assessing the strength and credibility of different kinds of postmarketing evidence and deciding how to weigh that evidence in making regulatory decisions.

When a meta-analysis raised the alarm about Avandia in 2007, FDA lacked such tools to assess drug safety and weigh postmarket evidence. As a result, the agency was unable to fight public and political pressure that eventually killed Avandia and imposed burdensome requirements for CV testing on all new diabetes candidates.

After six years, one 4,447-patient CV outcomes study and a third-party re-analysis of that study, the findings of the 2007 meta-analysis were invalidated. Both analyses of the RECORD study showed no increased CV risk for Avandia (see BioCentury, June 10).

But the damage had already been done. Avandia lost 99% of its sales, which fell to £6 million ($9 million) in 2012 from £1.4 billion ($2.2 billion) in 2006.

Additionally, FDA finalized guidance requiring companies developing any diabetes compound to rule out at least a 30% increase in CV risk before approval based on pooled results from Phase II and Phase III trials. A cardiovascular outcomes trial is then required postapproval.

In an op-ed published Sept. 2 in the New England Journal of Medicine, William Hiatt, Sanjay Kaul and Robert Smith said FDA’s 2008 guidance on development of diabetes drugs should apply only to compounds with a mechanism of action or side effect profile that could reasonably be expected to confer CV risk.

Hiatt is a cardiologist at the University of Colorado School of Medicine and president of the Colorado Prevention Center. Kaul is director of the fellowship training program in cardiovascular diseases at Cedars-Sinai Medical Center’s Heart Institute and a professor at the David Geffen School of Medicine at UCLA. Smith is a professor at the Alpert Medical School of Brown University.

At a June advisory meeting that reviewed the readjudicated results from RECORD and finally cleared Avandia, Hiatt voted to remove restrictions on the drug. Kaul voted to ease restrictions and Smith voted to keep the current restrictions in place.

Restrictions on Avandia include a REMS with a restricted distribution system.

Last week, Hiatt told BioCentury that a diabetes candidate with a mechanism of action unassociated with CV risk should be given a pass on the guidance.

“If a new drug is designed to lower glucose that maybe absorbs glucose in the gut, there is no reason to think there would be a CV concern. But if a drug has a mechanism of action or side effects that increase risk factors like blood pressure or cholesterol, a closer look should be taken,” he said.

Sentinel sounds

Whatever FDA does or does not do about its diabetes guidance, the bigger question is how it can deal more quickly with postmarket safety signals from a variety of sources — especially with data transparency efforts underway in Europe and the U.S. that could increase the volume of third-party analyses (see BioCentury, July 22).

Sentinel is one initiative that could help more quickly assess postmarketing safety signals.

Sentinel was started to fulfill the agency’s requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007, which called for active postmarket safety and surveillance of medical products.

FDA has developed Sentinel in stages, including preliminary work with the Veterans Health Administration to use VHA databases to identify drug risks, as well as with NIH to develop MedWatch plus, a public web portal to capture adverse event reports from the public and healthcare professionals (see BioCentury, April 21, 2008).

Now, the agency has developed and begun to use a pilot system called Mini-Sentinel.

FDA has used Mini-Sentinel to conduct postmarket reviews of at least two drugs — Pradaxa dabigatran etexilate from Boehringer Ingelheim GmbH and RotaTeq rotavirus vaccine from Merck & Co. Inc.

In October 2010, FDA approved Pradaxa to prevent stroke and clots in patients with atrial fibrillation. The agency then received what it described as “a large number of post-marketing reports of bleeding among Pradaxa users.” FDA did not specify the number of reports it had received.

To address the concerns, the agency reviewed insurance claims and administrative data from Mini-Sentinel to compare the rates of gastrointestinal bleeding and intracranial hemorrhage in new users of Pradaxa vs. new users of the anticoagulant warfarin.

In November 2012, FDA announced its findings: the com-
bined incidence rate of bleeding was actually 1.8-2.6 times higher for new users of warfarin vs. Pradaxa. P-values were not disclosed.

FDA is using the Mini-Sentinel system for two additional protocol-based observational studies of Pradaxa. In an email to BioCentury, the agency said it is making “progress” on the studies, but would not disclose expected completion dates.

The agency’s response to concerns about Pradaxa took two years, but, according to the program’s website, Mini-Sentinel is building the capacity to respond to many of FDA’s safety questions “within days or weeks.”

FDA also has taken action based on results from the Post-licensure Rapid Immunization Safety Monitoring Study (PRISM), a program within Mini-Sentinel focused on vaccine safety surveillance.

In June, FDA updated the label for Merck’s RotaTeq vaccine to note an increased risk of intussusception in the 21 days after the first dose based on PRISM data from more than 1.2 million RotaTeq vaccinations, including 507,000 first doses, in infants 5-36 weeks of age. The previous RotaTeq label noted an increased risk within the first 31 days.

PRISM includes data from more than 110 million individuals with 254 million person-years of observation time.

Mark McClellan, senior fellow and director of the Health Care Innovation and Value Initiative at the Brookings Institution, said that once Sentinel is fully operational, it should be able to shave years off assessing the potential risks of a drug.

“In principle, it could take only weeks or months,” he said. “The idea is real-time surveillance of over 100 million Americans. This is a much larger number than the initial meta-analyses and a more diverse group of people than with the initial reports of Avandia.”

McClellan added that while Sentinel can more quickly identify a signal, it is still a challenge to confirm the causal relationship between an adverse event and a drug. “Even observational data on 100 million Americans may not help you solve it,” he said.

Randomized, controlled postmarketing trials thus may be required in some cases.

In addition to Sentinel, FDA is finalizing its benefit-risk framework to characterize the uncertainties in benefits and risks of drugs both pre- and postapproval (see BioCentury, March 25).

During FY13, which ends Sept. 30, FDA has been working on a systematic approach for weighing postmarketing data from sources such as observational studies, controlled clinical trials and meta-analyses, and determining how to interpret the findings based on the weight assigned.

The approach will specify the sources of evidence, assess the strength of each piece of evidence, and draw conclusions that explain how any uncertainty weighed on subsequent decisions.

FDA would not say when it expects to finalize details of the new approach to weighing postmarket data.

In a written statement to BioCentury last week, FDA said it is also drafting guidance on best practices for meta-analyses.

“FDA hopes that the guidance will help establish best practices that can be followed by academic investigators, sponsors and FDA in the conduct of meta-analyses designed to seek new information about marketed drugs,” the agency said.

FDA added: “It is important that everyone involved in the development and analysis of information derived from meta-analyses be responsible in their reporting of these data and the conclusions that may be drawn, keeping in mind that there are many examples of where the findings of meta-analyses, even if well-conducted, are not borne out by the results of well-controlled clinical trials.”

FDA has authority under FDAAA to require additional postmarket studies if safety concerns arise, and to establish a timeline for when these should be completed.

The agency also said it is improving the ways it communicates safety information to the public, including being clear when there are uncertainties about risk.

**COMpanies and institutions mentioned**

- **Alpert Medical School of Brown University**, Providence, R.I.
- **Boehringer Ingelheim GmbH**, Ingelheim, Germany
- **Brookings Institution**, Washington, D.C.
- **Cedars-Sinai Medical Center**, Los Angeles, Calif.
- **Colorado Prevention Center**, Aurora, Colo.
- **David Geffen School of Medicine at UCLA**, Los Angeles, Calif.
- **GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.
- **Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.
- **National Institutes of Health** (NIH), Bethesda, Md.
- **U.S. Food and Drug Administration** (FDA), Silver Spring, Md.
- **University of Colorado School of Medicine**, Aurora, Colo.
- **Veterans Health Administration**, Washington, D.C.

**BioCentury makes people think**

There is only one journal — BioCentury, the Bernstein Report on BioBusiness™ — that is recognized by key decision makers as the best source of perspective, interpretation and analysis for top managers and investors in the biotech community.
Finance

Amgen’s poker face

By Michael Flanagan
Senior Writer

SEC filings posted last week detailing the negotiations between Amgen Inc. and Onyx Pharmaceuticals Inc. show that Amgen managed to shave more than $400 million off the final price based on interim Phase III data for multiple myeloma drug Kyprolis carfilzomib.

The data from the FOCUS trial, which emerged in late July, also scared off the only other offer Onyx was still seriously entertaining.

What was known prior to the filing was that Amgen made an unsolicited offer to buy Onyx for $120 per share in June; Onyx rejected the bid but put itself up for sale; and there had been multiple “interested” parties.

Amgen and Onyx agreed to a deal at $125 on Aug. 26. The small difference between the opening and final prices led some buysiders to conclude Amgen had preemptively priced other bidders out of the running (see BioCentury, July 15).

However, the SEC filings indicate there were two other bidders.

One was offering Onyx $35 per share in cash and a 45% stake in a combined company, but Onyx repeatedly informed this bidder, beginning on July 24, that it wanted an all-cash transaction.

The other bidder had offered $125-$130 in cash.

The documents also confirm Amgen’s previously rumored willingness to boost its bid to $130. According to the filings, Amgen made a non-binding offer to pay $130 on July 30, just days before Onyx told it and two other bidders about FOCUS.

The Phase III trial is evaluating overall survival for Kyprolis as a single agent in MM patients who have received three or more prior therapies. The drug has accelerated approval in the U.S.

In late July Onyx’s DMC took a planned interim look at the data and found Kyprolis had not met the criteria for stopping the study early.

The bidder that had offered $125-$130 in cash dropped out.

While Onyx shareholder Dallas Webb of BB Biotech told BioCentury that in his opinion the FOCUS news was a non-event, Amgen either felt differently — or was savvy enough to act like it did — dropping its offer to $121.

According to the filing, Onyx “did not agree that the DMC’s recommendation for the continuance of the FOCUS study could account for a $9 per share decrease.” It countered with $126 plus a CVR tied to data from ongoing trials that together could value the company at more than $130 per share.

The communications between the bankers — Lazard and BofA Merrill Lynch on the Amgen side; Centerview Partners for Onyx — made clear the bellwether had capped its price.

“Representatives from Lazard informed Centerview that Amgen was prepared to increase its offer above $121 per share in cash, but that it was not willing to make an offer of $126 per share in cash (with or without CVRs),” the Onyx filing stated.

Amgen upped the offer to $125 and refused Onyx’s last ditch request to up the bid to $126 without a CVR.

The final price values Onyx at $10.7 billion, about $400 million less than the $11.1 billion Amgen would have paid at $130.

Even so, several of Onyx’s top executives will make out quite well.

Tony Coles, who joined Onyx in 2008 as president and CEO and became chairman in 2012, will receive $58.1 million from the sale of stock, including $2.6 million from shares and $55.5 million in unvested shares, units and awards, according to an SEC filing.

Coles also is eligible for a $3.4 million cash severance payment.

Juergen Lasowski, EVP of corporate development and strategy who also joined the company in 2008, is in line for $27.1 million from the sale of stock and options.

EVP and CFO Matthew Fust, who joined the company in 2009, will receive $21.5 million.

The fourth largest payday of $7.3 million will go to Wendell Wierenga, who has served as a director since 1996. He is EVP of R&D at specialty pharma Santarus Inc.

In fact, the only member of Onyx’s executive team or its board who is not in line for a seven-figure payout is Antonio Grillo-Lopez, former chairman of the Neoplastic and Autoimmune Diseases Research Institute who has served as a director since 2002. He will receive $475,726.

The deal is expected to close by early 4Q13.

Amgen was up $2.15 last week to $111.01, while Onyx was up $0.33 to $123.93.

COMPANIES AND INSTITUTIONS MENTIONED

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Neoplastic and Autoimmune Diseases Research Institute, Rancho Santa Fe, Calif.
Onyx Pharmaceuticals Inc. (NASDAQ:ONXX), South San Francisco, Calif.
Santarus Inc. (NASDAQ:SNTS), San Diego, Calif.

‘It’s the BioCentury’

Authoritative. Globally focused. The leading perspective on the strategic issues essential to the formation, development and sustainability of life science ventures into 2013 and beyond.
Ebb & Flow

E round in the hand vs. IPO in the bush

By Michael Flanagan & Stephen Hansen
Senior Writers

The stars have yet to align for Argos Therapeutics Inc.'s pursuit of a public listing. An IPO attempt last year fizzled in poor market conditions, and when the window opened several months ago, the company already had lined up a series E round.

Argos closed the $42.5 million series E on Aug. 26. It hopes to raise $17.5 million in a second close within 60 days, said CEO Jeff Abbey. The company added two strategic investors: Pharmstandard OJSC (RTS:PHST; LSE:PHST), and Green Cross Corp. (KSE:006280).

Existing investors Forbion Capital; TVM Capital; Lumira Capital; Intersouth Partners; Caisse de depot et placement du Quebec; Morningside Group; and Aurora Funds participated.

The financing puts the immunotherapy play on sounder footing without precluding another run at a public exit as early as 2014.

“We tested the IPO market last year but our timing could not have been worse” from a market standpoint, noted Abbey. “We hadn’t started our Phase III trial so our timeline was basically too long for the public investors.”

Argos shelved the IPO in March 2012 and raised $25 million from existing investors a month later. The funds were enough to start a 450-patient Phase III trial of AGS-003 in January.

AGS-003 is a second-generation RNA-loaded autologous dendritic cell therapy to treat metastatic renal cell carcinoma (RCC).

The study will be fully enrolled in 2H14 with data expected by early 2016.

As 2012 wound to a close, Argos found it needed more money but still faced an unreceptive public market.

“We decided the best and fastest way to fund the company was through another private round.”

Jeff Abbey, Argos

Early stage attraction

Biotechnology Value Fund wanted to own a piece of what the firm thinks is one of the few pure drug discovery platforms remaining in the industry and thus invested €30 million ($40.2 million) to get a slice of Evotec AG (Xetra:EVT).

According to the firm’s Matthew Perry, an industry shift toward more product-focused business models has allowed Evotec to position itself as a drug discovery partner of choice.

“Evotec is in an incredible sweet spot of having built a world class drug discovery organization in an environment where everyone else is cutting back,” Perry told BioCentury. “They’ve done a lot of great deals.”

The company has at least 21 disclosed drug discovery or development deals with partners that include the Genentech Inc. unit of Roche (SIX:ROG; OTCQX:RHHBY), Johnson & Johnson (NYSE:JNJ) and Harvard University.

Evotec also has built multiple early stage partnerships with academia.

“In the old model academia would take an asset or target to a certain stage of development and then investors would start a new company to harness that technology and take it to the next stage,” Perry said. “Many of those companies don’t work because as a one-off bet, they are risky.”

Perry said Evotec has been able to aggregate these early stage translational deals, thus reducing the risk (see SciBX: Science-Business eXchange, Jan. 31).

BVF purchased 11.8 million shares at €2.55, a 4% discount to Evotec’s closing price of €2.67 on Aug. 29, the day before the deal was announced.

BVF also purchased from existing investor TVM Capital an option to acquire an additional 11.8 million Evotec shares at €4 within the next 30 months. If the option is fully exercised BVF would have an 18% stake and be the company’s largest shareholder.

For the week, Evotec rose €0.26 (10%) to €2.88, with a market cap of €341 million ($450 million).

Banker tracks

Matthew McAskin joined Evercore Partners as a senior managing director in the firm’s healthcare investment banking group. McAskin was a managing director and co-head of healthcare services investment banking at Goldman Sachs.

See next page
Buyside tracks

Carl Harald Janson was named investment manager for SV Life Sciences’ International Biotechnology Trust. He was investment manager at Karolinska Development, where he held various chief executive roles for portfolio companies.

Hedge fund tracks

Mitchell Gold and David Miller launched biotech hedge fund Alpine BioVentures. Gold, who is the founder and managing partner of Alpine, last year left prostate cancer play Dendreon Corp. (NASDAQ:DNDN), where he was president and CEO. Gold also founded and is chairman of next-gen cancer immunotherapy company Alpine Biosciences Inc.

Miller, a portfolio manager at Alpine BioVentures, was CEO of biotech research firm Biotech Stock Research.

Private equity tracks

Hanspeter Spek joined Advent International as a member of the firm’s operating partner program. He was president of global operations at Sanofi (Euronext:SAN; NYSE:SNY).

Venture tracks

The Baird Capital investment arm of Robert W. Baird & Co. added David Gregorka as a venture partner and Nicole Walker as a director. The two will join the venture capital group and focus on healthcare. Gregorka co-founded HealthMedia, now the Wellness & Prevention Inc. unit of Johnson & Johnson (NYSE:JNJ). Walker was director of venture investments for Abbott Ventures.

Regulatory milestones

ALK-Abello A/S (CSE:ALK-B) gained DKK8.50 to DKK482 last week after reporting that FDA’s Allergenic Products Advisory Committee will meet on Nov. 6 to discuss a BLA from partner Merck & Co. Inc. (NYSE:MRK) for grass Allergy Immunotherapy Tablet (AIT). Merck, which has North American rights, expects a decision in 1Q14. ALK-Abello markets grass AIT as Grazax in Europe.

Ariad Pharmaceuticals Inc. (NASDAQ:ARIA) gained $3.71 (20%) to $22.31 last week after saying it has enrolled about 264 of a planned 500 patients in the Phase III EPIC trial of Iclusig ponatinib to treat newly diagnosed chronic myelogenous leukemia (CML). Ariad plans to complete enrollment by year end and conduct an interim efficacy analysis in 3Q14.

FDA granted accelerated approval to Iclusig in December to treat CML and Philadelphia-chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) that is resistant or intolerant to prior treatment with tyrosine kinase inhibitors (TKIs). The EC approved the drug for the same indications in July.

Celgene Corp. (NASDAQ:CELG) added $1.38 to $146.97 on Friday after FDA approved an sNDA to expand the label of Abraxane nab-paclitaxel to include first-line treatment of advanced pancreatic cancer in combination with gemcitabine.

Abraxane is under review for pancreatic cancer in the EU. It is approved in the U.S. for first-line treatment of advanced non-small cell lung cancer (NSCLC), and in the U.S., EU and at least 12 other countries as second-line treatment of metastatic breast cancer.

Celgene was up $6.99 on the week.

Chelsea Therapeutics International Ltd. (NASDAQ:CHTP) was up $0.23 to $3.20 last week after providing an update on the PDUFA date for Northera droxidopa to treat symptomatic neurogenic orthostatic hypotension (NOH). The company said the new PDUFA date is Feb. 14; the original date was Jan. 3. In July, Chelsea said FDA identified undisclosed technical deficiencies with the application, which the company said would delay the PDUFA date.

Endo Health Solutions Inc. (NASDAQ:ENDP) was up $2.04 to $43.13 last week after FDA accepted for review a resubmitted NDA for Aveed testosterone to treat male hypogonadism. The PDUFA date is Feb. 28.

In a May complete response letter, FDA requested that Aveed’s REMS include a medication guide and elements to assure safe use (ETASU) “to mitigate the risks and severe complications related to post-injection reactions.”

Endo has U.S. rights to Aveed from Bayer AG (Xetra:BAYN).

Halozyme Therapeutics Inc. (NASDAQ:HALO) rose $0.67 to $8.98 last week after the European Commission approved a subcutaneous formulation of Herceptin trastuzumab from Roche (SIX:ROG; OTCQX:RHHBY) to treat HER-positive breast cancer. The product uses Halozyme’s Enhance recombinant human hyaluronidase (rHuPH20) drug delivery technology.

Theravance Inc. (NASDAQ:THRX) was up $0.81 to $37.52 on Friday after FDA reviewers said Anoro Ellipta umeclidinium/vilanterol from the biotech and GlaxoSmithKline plc (LSE:GSK; NYSE:GSK) is effective for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The comments came in briefing documents for the Pulmonary-Allergy Drugs Advisory Committee meeting on Tuesday this week to discuss the NDA, which has a Dec. 18 PDUFA date.

Earlier in the week, Theravance’s TD-4208 met the primary endpoint in a Phase IIb trial to treat COPD. The compound is an inhaled long-acting muscarinic antagonist (LAMA) (see B19).

Theravance was up $1.67 on the week.

Zealand Pharma A/S (CSE:ZEAL) edged up DKK4 to DKK66.50 last week after Germany’s Federal Joint Committee (G-BA) said in a final benefit assessment that Type II diabetes drug Lyxumia lixisenatide has “no additional benefit” over comparators.

Lyxumia is under review in the U.S. with an undisclosed PDUFA date.

Clinical milestones

Agenus Inc. (NASDAQ:AGEN) fell $0.89 (24%) to $2.82 on Thursday after GlaxoSmithKline plc (LSE:GSK; NYSE:GSK) said cancer vaccine MAGE-A3 given after surgical removal of a patient’s tumors missed the co-primary endpoint of disease-free survival (DFS) in a Phase III trial to treat melanoma-associated antigen A3 (MAGEA3)-positive, resected melanoma.

GSK said it will continue the trial until assessing the second co-primary endpoint, DFS in a patient subgroup; those data are expected in 2015 (see B6).

The treatment incorporates QS-21 Stimulon adjuvant from Agenus, which was down $0.79 (22%) to $2.86 on the week.

ArQuile Inc. (NASDAQ:ARQL) slid $0.30 (11%) to $2.49
on Tuesday after disclosing that a DMC recommended reducing the dose of tivantinib in a Phase III trial to treat inoperable hepatocellular cancer (HCC). The recommendation followed a higher incidence of neutropenia than was seen in a Phase II trial (see B20).

ArQule continued to tumble to finish the week off $0.55 (20%) to $2.24.

Cytokinetiks Inc. (NASDAQ:CYTK) fell $2.82 (27%) to $7.65 on Tuesday after it and partner Agen Inc. (NASDAQ: AMGN) said omecamtiv mecarbil given as an IV infusion missed the primary endpoint in the Phase Ib IIb ATOMIC-AHF trial to treat patients with left ventricular systolic dysfunction hospitalized for acute heart failure (see B14).

Data from the Phase II COSMIC-HF trial evaluating an oral formulation in patients with chronic heart failure (CHF) and left ventricular systolic dysfunction are expected in H14.

Cytokinetiks gained back some ground to end the week down $1.91 (18%) to $8.56.

Rockwell Medical Technologies Inc. (NASDAQ:RMTI) gained $2.74 (50%) to $8.27 last week after reporting that Soluble Ferric Pyrophosphate (SFP) met the primary endpoint in the CRUISE-2 Phase III trial to treat iron deficiency anemia in chronic kidney disease (CKD) patients requiring hemodialysis (see B19).

In July, Rockwell reported that SFP met the primary endpoint in the identical Phase III CRUISE-I trial. The company plans to submit an NDA to FDA around 1Q14.

Transgene S.A. (Euronext:TNG) fell €1.36 (13%) to €8.90 on Wednesday after Pexa-Vect (JX-594) as second-line treatment missed the primary endpoint in a Phase Ib IIb trial to treat advanced hepatocellular carcinoma (HCC) (see B17).

Transgene said it will determine next quarter whether to move Pexa-Vect into Phase III testing for first-line HCC. Pexa-Vect is a recombinant vaccinia virus that expresses GM-CSF and lacks thymidine kinase.

Transgene finished the week down €1.50 (15%) to €8.50.

Ebb & Flow

Algeta ASA (OSE:ALGETA) was off NOK18.8 to NOK239 last week after raising $120 million through the sale of convertible senior unsecured bonds due 2018. The bonds bear a 3.4% coupon and initially convert at $52.50.

Algeta and partner Bayer AG (Xetra:BAYN) market Xofigo radium-223 dichloride in the U.S. to treat castration-resistant prostate cancer (CRPC) in patients with symptomatic bone metastases.

Diagnostics company bioMerieux S.A. (Euronext:BIM) was up €0.03 to €75.75 last week after saying it will acquire BioFire Diagnostics Inc. for $450 million in cash. bioMerieux also will assume an undisclosed amount of BioFire’s net debt.

BioFire develops and markets in vitro tests for its multiplex PCR FilmArray system. The deal is expected to close by year end or in early 2014.

BioPorto Diagnostics A/S (CSE: BIOPOR) was up DKK0.31 (23%) to DKK1.66 on Friday after raising DKK70.7 million ($12.5 million) through the sale of 70.7 million shares at DKK1 in a rights offering. BioPorto, which proposed the offering in late May, markets its NGAL Test to diagnose acute kidney injury in Canada and the EU.

BioPorto was up DKK 0.46 (38%) to DKK1.66 on the week.

Catalyst Pharmaceuticals Partners Inc. (NASDAQ: CPRX) added $0.16 to $2.10 last week after raising $15.1 million through the sale of 8.8 million shares at $1.72 in a registered direct offering. The price is an 11% discount to Catalyst’s close of $1.94 on Sept. 4, before the offering was announced.

Catalyst’s shares are up $0.68 (48%) since Aug. 26, before the company announced FDA granted breakthrough therapy designation to the company’s Firdapse amifampridine to treat Lambert-Eaton myasthenic syndrome (LEMS). Firdapse is in Phase III testing, with data expected in 2Q14.

Cubist Pharmaceuticals Inc. (NASDAQ: CBST) gained $0.50 to $63.86 last week after raising $700 million through the sale of convertible senior unsecured notes to institutional investors to fund its acquisition of fellow infectious disease company Optimer Pharmaceuticals Inc. (NASDAQ:OPTR).

Last month, Cubist announced plans to acquire Optimer as well as another infectious disease play, Trius Therapeutics Inc. (NASDAQ:TSRX), in cash and contingent value right (CVR) deals potentially worth up to $1.6 billion in total.

Ironwood Pharmaceuticals Inc. (NASDAQ:IRWD) gained $1.15 (10%) to $12.80 last week after Maxim’s Jason Kolbert in an analyst note downgraded competitor Sucampo Pharmaceuticals Inc. (NASDAQ:SCMP) from “buy” to “hold” and lowered his price target on Sucampo to $7 from $9 (see Analyst Picks, A20).

Kolbert cited an article in BioCentury reviewing Ironwood’s pricing strategy (see BioCentury, Sept. 2).

Sucampo was off $0.11 to $5.81 on the week.

Pozen Inc. (NASDAQ: POZN) gained $0.56 (11%) to $5.85 on Thursday after granting Sanofi (Euronext:SAN; NYSE:SNY) U.S. rights to PA32540 and its lower dose formulation, PA8140, for $15 million up front and up to $20 million in pre-commercial milestones, plus undisclosed milestones and royalties. A combined NDA for the products is under FDA review for the secondary prevention of cardio-
vascular disease in patients at risk for aspirin-induced gastric ulcers; the PDUFA date is Jan. 24.

The products are tablets comprising aspirin and an immediate-release coating of 40 mg omeprazole.

Pozen finished the week up $0.50 (10%) to $5.67.

ThromboGenics N.V. (Euronext:THR) tacked on €0.02 to €22.94 last week after receiving exclusive rights to develop and commercialize bicyclic peptide inhibitors from Bicycle Therapeutics Ltd. against an undisclosed target involved in ophthalmic diseases like diabetic macular edema (DME). Bicycle will receive an undisclosed upfront fee and is eligible for undisclosed milestones, plus royalties.

Vivus Inc. (NASDAQ:VVUS) lost $1.57 (13%) to $10.96 last week after Anthony Zook resigned as CEO and a director for medical reasons. The biotech hired Seth Fischer as CEO and a director to replace Zook. Fischer retired as company group chairman at Johnson & Johnson (NYSE:JNJ) and worldwide franchise chairman at the pharma’s Cordis Corp. subsidiary last year.

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

<table>
<thead>
<tr>
<th>Company</th>
<th>Bank</th>
<th>Analyst</th>
<th>Coverage</th>
<th>Opinion</th>
<th>Wk chg</th>
<th>9/6 cls</th>
<th>Wk chg</th>
<th>9/6 cls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacyclics Inc.</td>
<td>Lazard</td>
<td>Joshua Schimmer</td>
<td>Upgrade</td>
<td>Buy (from neutral)</td>
<td>6%</td>
<td>$117.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resverlogix Corp.</td>
<td>MLV</td>
<td>George Zavoico</td>
<td>Upgrade</td>
<td>Hold (from sell)</td>
<td>6%</td>
<td>C$0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucampo Pharmaceuticals</td>
<td>Maxim Group</td>
<td>Jason Kolbert</td>
<td>Downgrade</td>
<td>Hold (from buy)</td>
<td>-2%</td>
<td>$5.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vivus Inc. (NASDAQ:VVUS)</td>
<td>Lazard</td>
<td>Joshua Schimmer</td>
<td>Downgrade</td>
<td>Sell (from neutral)</td>
<td>-13%</td>
<td>$10.96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analyst picks & changes

We know you have many choices for headlines. But finding real intelligence is a lot harder. That’s why top managers and investors in the life sciences community depend on BioCentury, the Bernstein Report on BioBusiness™ for its leading perspective on the strategic issues essential to the formation, development and sustainability of life science ventures in 2013 and beyond.

‘It’s the BioCentury’™
Astex Pharmaceuticals Inc. (NASDAQ:ASTX) ended the week up 33% on the announcement that the Otsuka Pharmaceutical Co. Ltd. subsidiary of Otsuka Holdings Co. Ltd. (Tokyo:4478) will acquire the biotech for $8.50 per share in cash, or $866 million. Astex shares are up nearly 200% since its formation from the merger between Astex Therapeutics Ltd. and SuperGen Inc. in July 2011.

Over the last two years, Astex has made good on Chairman and CEO James Manuso’s goal outlined at the time of the merger of becoming a mid-tier cancer play valued between $500 million and $1 billion. Astex’s market cap after the deal was $272.8 million.

The merged company was slow out of the gates, as the company encountered regulatory setbacks in the U.S. in efforts to expand the label for Dacogen decitabine in acute myelogenous leukemia (AML). However, the stock moved up in 2H12 following EU approval of the hypomethylating agent for the new indication.

Astex shares gained 24% on Aug. 28 after the company said subcutaneous once-daily SGI-110, a second-generation version of Dacogen, led to an overall remission rate of 25% in 67 evaluable AML patients in the Phase II portion of the Phase I/II SGI-110-01 trial to treat myelodysplastic syndrome (MDS) and AML.

Dacogen is already approved in the U.S. to treat MDS. Eisai Co. Ltd. (Tokyo:4523; Osaka:4523) markets Dacogen in North America under a license from Astex. Johnson & Johnson (NYSE:JNJ) has rights elsewhere from Eisai. Selected events tracked against Astex’s daily share price below. Source: BCIQ: BioCentury Online Intelligence

A. 7/20/11 — SuperGen Inc. completes acquisition of Astex Therapeutics Ltd. for $25M in cash, plus shares representing 35% of the combined company. Astex shareholders were to receive an additional $30M in stock or cash over 30 months. Company is renamed Astex Pharmaceuticals Inc. (NASDAQ:ASTX).

B. 1/16/12 — Astex ends 2009 deal with GlaxoSmithKline plc (LSE:GSK; NYSE:GSK) to discover cancer therapeutics based on epigenetic targets. The decision was made after discussions with GSK and a review of Astex’s internal pipeline following the merger.

C. 2/9/12 — FDA’s Oncologic Drugs Advisory Committee (ODAC) votes 10-3, with one abstention, that Dacogen did not demonstrate a favorable benefit-risk profile to treat newly diagnosed AML in patients 65 years and older.

D. 3/7/12 — FDA issues a complete response letter for an sNDA from Eisai for Dacogen to treat AML. According to the partners, FDA declined to approve the application because Dacogen did not show a statistically significant improvement in overall survival (OS) over low-dose cytarabine or supportive care in the Phase III DACO-016 trial (p=0.11).

E. 7/20/12 — EMA’s CHMP recommends approval of an MAA from partner Johnson & Johnson for Dacogen to treat newly diagnosed de novo or secondary AML in patients 65 years and older.

F. 9/28/12 — EC approves Dacogen to treat newly diagnosed de novo or secondary AML in patients 65 years and older.

G. 5/2/13 — Germany’s Federal Joint Committee (G-BA) says Dacogen has a “marginal” additional benefit to treat newly diagnosed de novo or secondary AML in patients 65 years and older.

H. 8/28/13 — Astex up $1.34 (24%) to $6.82 after reporting that subcutaneous once-daily SGI-110 led to an overall remission rate of 25% in 67 evaluable AML patients in the Phase II portion of the Phase I/II SGI-110-01 trial to treat MDS and AML.

I. 9/5/13 — Otsuka proposes to acquire Astex for $8.50 per share in cash, or $866M.
BioCentury tracks 617 issues that report prices and volume daily. The BioCentury 100 is a subset used to monitor price and volume trends.

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

### Price Gains
Stocks with greatest % price increase in the week ended Sept. 6. (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>Inovio</td>
<td>INO</td>
<td>2.430</td>
<td>0.730</td>
<td>43%</td>
<td>484059</td>
</tr>
<tr>
<td>Astex Pharma</td>
<td>ASTX</td>
<td>8.730</td>
<td>2.180</td>
<td>33%</td>
<td>804769</td>
</tr>
<tr>
<td>GW Pharma¹</td>
<td>GWPH</td>
<td>16.400</td>
<td>3.980</td>
<td>32%</td>
<td>65568</td>
</tr>
<tr>
<td>Cellular Dynamics</td>
<td>ICEL</td>
<td>17.040</td>
<td>3.980</td>
<td>30%</td>
<td>2605</td>
</tr>
<tr>
<td>CanBas</td>
<td>4575</td>
<td>¥1174.00</td>
<td>¥222</td>
<td>23%</td>
<td>4707</td>
</tr>
<tr>
<td>Insys</td>
<td>INSY</td>
<td>33.820</td>
<td>5.810</td>
<td>17%</td>
<td>10438</td>
</tr>
<tr>
<td>Ariad</td>
<td>ARIA</td>
<td>22.310</td>
<td>3.710</td>
<td>17%</td>
<td>152712</td>
</tr>
<tr>
<td>Intrexon</td>
<td>XON</td>
<td>25.540</td>
<td>3.810</td>
<td>18%</td>
<td>21992</td>
</tr>
<tr>
<td>Merrimack</td>
<td>MACK</td>
<td>3.970</td>
<td>0.590</td>
<td>17%</td>
<td>70044</td>
</tr>
<tr>
<td>NanoCarrier</td>
<td>4571</td>
<td>¥174600</td>
<td>¥23800</td>
<td>16%</td>
<td>886</td>
</tr>
<tr>
<td>Agios</td>
<td>AGIO</td>
<td>27.080</td>
<td>3.500</td>
<td>15%</td>
<td>3309</td>
</tr>
<tr>
<td>SymBio</td>
<td>4582</td>
<td>¥1442.00</td>
<td>¥57.00</td>
<td>15%</td>
<td>38000</td>
</tr>
<tr>
<td>Tetraphase</td>
<td>TTPH</td>
<td>9.780</td>
<td>1.240</td>
<td>15%</td>
<td>3156</td>
</tr>
<tr>
<td>Avanir</td>
<td>AVNR</td>
<td>5.840</td>
<td>0.740</td>
<td>15%</td>
<td>121377</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>Agenus</td>
<td>AGEN</td>
<td>2.860</td>
<td>-0.790</td>
<td>-22%</td>
<td>36788</td>
</tr>
<tr>
<td>ArQule</td>
<td>ARQL</td>
<td>2.240</td>
<td>-0.550</td>
<td>-20%</td>
<td>37267</td>
</tr>
<tr>
<td>Cytkinetics</td>
<td>CYTK</td>
<td>8.560</td>
<td>-1.910</td>
<td>-18%</td>
<td>101099</td>
</tr>
<tr>
<td>Transgene</td>
<td>TNG</td>
<td>€8.500</td>
<td>-€1.500</td>
<td>-15%</td>
<td>6623</td>
</tr>
<tr>
<td>Vivus</td>
<td>VVUS</td>
<td>10.960</td>
<td>-1.570</td>
<td>-13%</td>
<td>180838</td>
</tr>
<tr>
<td>Pacific Biosciences</td>
<td>PACB</td>
<td>3.660</td>
<td>-0.520</td>
<td>-12%</td>
<td>29959</td>
</tr>
<tr>
<td>Chembio</td>
<td>CEMI</td>
<td>3.351</td>
<td>-0.399</td>
<td>-11%</td>
<td>3501</td>
</tr>
<tr>
<td>Lexicon</td>
<td>LXRX</td>
<td>2.270</td>
<td>-0.220</td>
<td>-9%</td>
<td>36425</td>
</tr>
<tr>
<td>Opko²</td>
<td>OPK</td>
<td>8.490</td>
<td>-0.750</td>
<td>-8%</td>
<td>330533</td>
</tr>
<tr>
<td>Algeta</td>
<td>ALGETA</td>
<td>NOK239-NOK188</td>
<td>-7%</td>
<td>9496</td>
<td></td>
</tr>
<tr>
<td>Clovis</td>
<td>CLVS</td>
<td>60.260</td>
<td>-4.240</td>
<td>-7%</td>
<td>16670</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>IntegraGen</td>
<td>ALINT</td>
<td>158</td>
<td>31444%</td>
<td>€3.830</td>
<td>€0.00</td>
</tr>
<tr>
<td>PCI</td>
<td>PCIB</td>
<td>180</td>
<td>5345%</td>
<td>NOK20.3</td>
<td>-NOK0.6</td>
</tr>
<tr>
<td>OvaScience</td>
<td>OVAS</td>
<td>3512</td>
<td>1000%</td>
<td>1.3160</td>
<td>1.640</td>
</tr>
<tr>
<td>Probi</td>
<td>PROB</td>
<td>2035</td>
<td>59%1</td>
<td>SEK41.7</td>
<td>SEK1.4</td>
</tr>
<tr>
<td>Clingen Group</td>
<td>CLIN</td>
<td>3731</td>
<td>516%</td>
<td>372.5p</td>
<td>3.8p</td>
</tr>
<tr>
<td>SymBio</td>
<td>4582</td>
<td>38000</td>
<td>367%</td>
<td>¥442</td>
<td>¥57</td>
</tr>
<tr>
<td>Carina</td>
<td>4572</td>
<td>159</td>
<td>357%</td>
<td>¥79600</td>
<td>¥11000</td>
</tr>
<tr>
<td>Transgene</td>
<td>TNG</td>
<td>6623</td>
<td>353%</td>
<td>¥8500</td>
<td>-¥1500</td>
</tr>
<tr>
<td>Cubist</td>
<td>CBST</td>
<td>80586</td>
<td>296%</td>
<td>63.860</td>
<td>0.500</td>
</tr>
<tr>
<td>CanBas</td>
<td>4575</td>
<td>4707</td>
<td>295%</td>
<td>¥1174</td>
<td>¥222</td>
</tr>
</tbody>
</table>

1 Includes volume from London Stock Exchange with converted ADSs (1ADS = 12 shares)
2 Includes volume from Tel Aviv Stock Exchange

### BioCentury 100 Advance-Decline Trend

<table>
<thead>
<tr>
<th>Week ended</th>
<th>BC100 Price level</th>
<th>BC100 Stocks gaining</th>
<th>BC100 Stocks declining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug 09</td>
<td>4104.20</td>
<td>33</td>
<td>2878916</td>
</tr>
<tr>
<td>Aug 16</td>
<td>3961.21</td>
<td>16</td>
<td>1327727</td>
</tr>
<tr>
<td>Aug 23</td>
<td>4062.57</td>
<td>86</td>
<td>4771000</td>
</tr>
<tr>
<td>Aug 30</td>
<td>4045.20</td>
<td>33</td>
<td>3440084</td>
</tr>
<tr>
<td>Sep 06</td>
<td>4205.98</td>
<td>81</td>
<td>4444162</td>
</tr>
</tbody>
</table>

It’s accurate. It’s trusted.
It delivers.

Put the power of BioCentury’s team and 19 years of industry analysis and reporting behind your data solutions needs

Get a Free BCIQ Trial
www.biocentury.com/bciq

Intelligence you can trust. Because biopharma is our business.
The 20th Annual
NEWSMAKERS
IN THE BIOTECH INDUSTRY
September 27, 2013 • New York City
Millennium Broadway Hotel & Conference Center

Looking for Partnership Opportunities?
Then NewsMakers is for You

A Full Slate of Companies with
135 Unpartnered Products in 225 Programs

Final Slate of Presenting Companies

- Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY)
- AMAG Pharmaceuticals Inc. (NASDAQ:AMAG)
- Ambit Biosciences Corp. (NASDAQ:AMBI)
- Arena Pharmaceuticals Inc. (NASDAQ:ARNA)
- Array BioPharma Inc. (NASDAQ:ARRY)
- BioMarin Pharmaceutical Inc. (NASDAQ:BMRN)
- Cempra Inc. (NASDAQ:CEMP)
- Chelsea Therapeutics International Ltd. (NASDAQ:CHTP)
- ChemoCentryx Inc. (NASDAQ:CCXI)
- Chimerix Inc. (NASDAQ:CMRX)
- Cytokinetics Inc. (NASDAQ:CYTK)
- Cytos Biotechnology AG (SIX:CYTN)
- Durect Corp. (NASDAQ:DRRRX)
- Epizyme Inc. (NASDAQ:EPZM)
- Esperion Therapeutics Inc. (NASDAQ:ESPR)
- Exelixis Inc. (NASDAQ:EXEL)
- Galenti (NASDAQ:GALT)
- Galena Biopharma Inc. (NASDAQ:GALE)
- Halozyme Therapeutics Inc. (NASDAQ:HALO)
- Horizon Pharma Inc. (NASDAQ:HZN)
- ImmunoCellular Therapeutics Ltd. (NYSE-M:IMUC)
- Inovio Pharmaceuticals Inc. (NASDAQ:INO)
- KaloBios Pharmaceuticals Inc. (NASDAQ:KBLI)
- Keryx Biopharmaceuticals Inc. (NASDAQ:KRX)
- The Medicines Co. (NASDAQ:MDCO)
- MEI Pharma Inc. (NASDAQ:MEPI)
- Mesoblast Ltd. (ASX:MSB; Pink:MBLY)
- Navidea Biopharmaceuticals Inc. (NYSE-M:NAV)
- Nektar Therapeutics (NASDAQ:NKTR)
- NeoStem Inc. (NASDAQ:NBS)
- NewLink Genetics Corp. (NASDAQ:NLNK)
- NPS Pharmaceuticals Inc. (NASDAQ:NPSP)
- Omnia Corp. (NASDAQ:OMER)
- OncoMed Pharmaceuticals Inc. (NASDAQ:OMED)
- Orexo AB (SSE:ORX)
- Organovo Holdings Inc. (NYSE-M:ONVO)
- Portola Pharmaceuticals Inc. (NASDAQ:PTRA)
- Prosensa Holding N.V. (NASDAQ:RNA)
- Receptos Inc. (NASDAQ:RCPT)
- Repros Therapeutics Inc. (NASDAQ:RPRX)
- Resveroxine Corp. (TSE:RXX)
- SciClone Pharmaceuticals Inc. (NASDAQ:SCLN)
- Sucampo Pharmaceuticals Inc. (NASDAQ:SMP)
- Sunesis Pharmaceuticals Inc. (NASDAQ:SNSS)
- TG Therapeutics Inc. (NASDAQ:TGX)
- TherapeuticsMD Inc. (NYSE-M:TXMD)
- Verastem Inc. (NASDAQ:VSTM)
- Zolipharm Oncology Inc. (NASDAQ:ZIO)

Special Thanks to Our Sponsors

For sponsorship opportunities, please email Eric Pierce at ericpierce@biocentury.com
Join Key Thought Leaders in Epigenetics
Building a Roadmap for Innovation
SciBX Summit • October 30, 2013 • Boston, MA

Featuring a World-Class Panel of Experts
Including Bruce Booth and Stuart Schreiber

Join Bruce Booth, Stuart Schreiber and our entire panel of experts and respondents from academia, biotech, pharma and the investment community at the SciBX Summit on Innovation in Drug Discovery & Development.

These key thought leaders in the Epigenetics space will examine potential challenges and opportunities in the field and jointly sketch an in-depth roadmap of new targets, pathways and approaches for treating disease.

"Epigenetics' Second Wind" is just one of the four 'can't-miss' tracks on the program at the SciBX Summit.

Panel of Experts

- James Audia, Ph.D. (Constellation Pharmaceuticals Inc.)
- Bruce Booth, Ph.D. (Atlas Venture and Rodin Therapeutics Inc.)
- Charles Roberts, M.D., Ph.D. (Harvard University)
- Stuart Schreiber, Ph.D. (Broad Institute)
- Jesse Smith, Ph.D. (Epizyme Inc.)
- Peter Tummino, Ph.D. (GlaxoSmithKline plc)

Respondents

- Simon Kerry, Ph.D. (Karus Therapeutics Ltd.)
- Don McCaffrey (Zenith Epigenetics Corp.)

ADVISORY COUNCIL MEMBERS

Amgen Inc.
AstraZeneca plc
Biogen Idec Inc.
GlaxoSmithKline plc
Merck & Co. Inc.
Novartis AG
Sanofi

TRACK SPONSORS

Acetylon Pharmaceuticals Inc.
Karus Therapeutics Ltd.
RaNA Therapeutics Inc.
Zenith Epigenetics Corp.
BIO-Europe® is Europe’s largest partnering conference, serving the global biotechnology industry. The conference annually attracts international leaders from biotech, pharma and finance along with the most promising start-ups and emerging companies. It is the “must attend” event for getting business done in the biotech industry.

For further information, please view our conference website at www.ebdgroup.com/bioeurope
BioCentury
WEEK IN REVIEW

BioBusiness for the week ended September 6

Using BioCentury Week in Review

You can read Week in Review online every Monday at www.biocentury.com

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

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

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

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

Clintagene (TSX-V:MBI)
Rigel (NASDAQ:RGLD)
SurModics (NASDAQ:SRDX)
Worldwide Innov Networking

Management Tracks (Page B9)

Acacia
Arsanis
Biocartis
Celgene (NASDAQ:CELG)
Champions Oncol (OTCBB:CSBR)
Chembio (NASDAQ:CEMI)
CollabRx (NASDAQ:CLRX)
GenVec (NASDAQ:GNVC)
Immune Design
Immunomedics (NASDAQ:IMMU)
Infinity Pharma (NASDAQ:INFI)
iPierian
iJ (NYSE:JNJ)
Kymab
Merck KGaA (Xetra:MRK)
Mind-NRG
Mirati (NASDAQ:MRTX)
Ocera (NASDAQ:OCRX)
Otsycline
True North Therap
Verona (LSE:VRP)
Vivus (NASDAQ:VVUS)
Zealand (CSE:ZEAL)

Clinical News

Regulatory (Page B11)

ALK-Abello (CSE:ALK-B)/Merck (NYSE:MRK)
Amgen (NASDAQ:AMGN)/Daiichi (Tokyo: 4568; Osaka:4568)
AstraZeneca (LSE:AZN; NYSE:AZN)/Bayer (Xetra:BAYN)
Bristol-Myers (NYSE: BMY)/Novartis (NYSE: NVS; SIX:NOVN)
Celgene (NASDAQ:CELG)/Taiho
Cheslea (NASDAQ:CHTP)/Dainippon (Tokyo:4506; Osaka:4506)
Csl (ASX:CSL)
Endo (NASDAQ:ENDP)/Bayer (Xetra:BAYN)
Genentech/Halozyme (NASDAQ:HALO)/Chugai (Tokyo:4519)/Roche (SIX:ROG; OTCQX:RHHBY)
DEALS

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

Onyx Pharmaceuticals Inc. (NASDAQ:ONXX), South San Francisco, Calif.

Business: Cancer

SEC filings from Amgen and Onyx outlined the discussions that led to the announcement in late August that Amgen will acquire Onyx for $125 per share in cash, or about $10.4 billion. Among the new details to emerge was that in late July, Amgen had upped to $130 its original, unsolicited bid of $120, which Onyx’s board rejected. However, Amgen then decreased its bid to $121 in early August after Onyx reported that multiple myeloma (MM) drug Kyprolis carfilzomib had not met the early stopping criteria in the ongoing Phase III FOCUS trial. Onyx countered that it would agree to $126 plus a contingent value right (CVR) tied to data from ongoing trials that Onyx said would value it at more than $130 per share, but Amgen rejected the offer.

Amgen’s acquisition of Onyx is expected to close by early 4Q13 (see BioCentury, Sept. 2).

Astex Pharmaceuticals Inc. (NASDAQ:ASTX), Dublin, Calif.

Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan

Business: Cancer

Otsuka will acquire Astex for $8.50 per share in cash, or about $866 million. The price is a 27% premium to Astex’s close of $6.68 on Sept. 3, before rumors surfaced that Otsuka was acquiring Astex for ¥90 billion ($913.5 million). The boards of both companies unanimously approved the deal, which is expected to close by early 4Q13.

Otsuka will gain Astex’s Pyramid fragment based screening technology and said the deal also will strengthen the pharma’s oncology portfolio. Johnson & Johnson (NYSE:JNJ, New Brunswick, N.J.) and Eisai Co. Ltd. (Tokyo:4523; Osaka:4523, Tokyo, Japan) market Astex’s myelodysplastic syndrome (MDS) drug Dacogen decitabine. Astex’s cancer pipeline also includes SG-110, a second-generation version of Dacogen in Phase II testing for MDS, acute myelogenous leukemia (AML), ovarian and liver cancer; and AT13387, a non-ansamycin inhibitor of heat shock protein 90 (Hsp90) in Phase II testing for gastrointestinal stromal tumours (GIST), prostate and lung cancers. Otsuka markets Busulfex busulfan as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia (CML), and the pharma also markets leukemia drug Sprycel dasatinib with Bristol-Myers Squibb Co. (NYSE:BMY, New York, N.Y.) in the U.S., EU and Japan. Astex reported $83.2 million in revenues for 2012. Parent Company Otsuka Holdings Co. Ltd. (Tokyo:4578, Tokyo, Japan) reported FY2012 sales of ¥850.9 billion ($10.3 billion) by the pharmaceutical business segment, which includes Otsuka Pharmaceuticals as well as other subsidiaries.

Jeffe was financial advisor to Astex, and Wilson Sonsini Goodrich & Rosati P.C. was the company’s legal advisor. Goldman Sachs was financial advisor to Otsuka Pharmaceuticals. Skadden, Arps, Slate, Meagher & Flom LLP was the company’s legal advisor.

Bicycle Therapeutics Ltd., Cambridge, U.K.

ThromboGenics N.V. (Euronext:THR), Leuven, Belgium

Business: Ophthalmic

Bicycle granted ThromboGenics exclusive rights to develop and commercialize bicyclic peptide inhibitors against a target involved in...

See next page

FINANCIAL NEWS

Completed Offerings (Page B23)

Acacia Pharma
Affinium
Algeta (OSE:ALGETA)
Arsanis
BioPorto (CSE:BIOPOR)
Catalyst (NASDAQ:CPRX)
ContraFect
Critical Outcome (TSX-V: COT)
Cubist (NASDAQ:CBST)

See next page
biosimilars of Enbrel are in development worldwide, including a U.S. and Canada, while Pfizer has rights elsewhere. Amgen reported Inc. (NYSE:PFE, New York, N.Y.) co-market Enbrel etanercept in the (May 14, 2012) Coherus said the biosimilar is in the “early clinical stages” Co. Ltd. (Tokyo:4568; Osaka:4568, Tokyo, Japan) under a 2012 deal. Coherus is already developing the biosimilar in Asia with Daiichi Sankyo receive $30 million up front and will be responsible for development, in Europe, Canada, Brazil and other undisclosed markets. Coherus will generate about $70 million in sales for the fiscal year ending Sept. 30, 2013. The deal is expected to close by year end or in early 2014.

BioFire Diagnostics Inc., Salt Lake City, Utah bioMerieux S.A. (Euronext:BIM), Marcy l’Etoile, France Business: Diagnostic Diagnostics company bioMerieux will acquire BioFire for $450 million in cash. bioMerieux also will assume an undisclosed amount of BioFire’s net debt. BioFire develops and markets in vitro tests for its multiplex PCR FilmArray system. The company markets its FilmArray Respiratory Panel in the U.S and EU to detect respiratory viruses and bacteria, and its FilmArray Blood Culture Identification Panel in the U.S. to detect and identify organisms that can cause sepsis and selected antibiotic resistance genes. bioMerieux said it expects BioFire to generate about $70 million in sales for the fiscal year ending Sept. 30, 2013. The deal is expected to close by year end or in early 2014.

Coherus BioSciences Inc., Redwood City, Calif. Baxter International Inc. (NYSE:BAX), Deerfield, Ill. Business: Biosimilars, Autoimmune Biosimilars company Coherus partnered with Baxter to develop and commercialize a biosimilar of autoimmune drug Enbrel etanercept in Europe, Canada, Brazil and other undisclosed markets. Coherus will receive $30 million up front and will be responsible for development, and Baxter will be responsible for commercialization. Coherus is eligible for up to $216 million in milestones, plus undisclosed royalties. Coherus is already developing the biosimilar in Asia with Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568, Tokyo, Japan) under a 2012 deal. Coherus said the biosimilar is in the “early clinical stages” (see BioCentury, May 14, 2012).

Amgen Inc. (NASDAQ:AMGN, Thousand Oaks, Calif.) and Pfizer Inc. (NYSE:PFE, New York, N.Y.) co-market Enbrel etanercept in the U.S. and Canada, while Pfizer has rights elsewhere. Amgen reported $4.2 billion in 2012 worldwide Enbrel sales. At least five other biosimilars of Enbrel are in development worldwide, including a biosimilar from the Sandoz generics unit of Novartis AG (NYSE:NVS; SIX:NOVN, Basel, Switzerland) that is in an international Phase III trial for moderate to severe chronic plaque-type psoriasis.

CordenPharma International GmbH, Plankstadt, Germany Solvay S.A. (Euronext:SOB), Brussels, Belgium Business: Other Contract manufacturing provider CordenPharma will acquire Solvay’s Peptisyntha S.A. business, which manufactures custom peptides for pharmaceutical use. The deal, which does not include U.S. sister company Peptisyntha Inc., is expected to close later this fall. Peptisyntha will become CordenPharma’s third site offering peptide manufacturing. The companies could not be reached for details. The deal completes Solvay’s exit from life science activities. In 2010, the group sold its pharmaceuticals business to Abbott Laboratories (NYSE:ABT, Abbott Park, Ill.). Abbott spun out its pharmaceuticals business into newco AbbVie Inc. (NYSE:ABBV, Chicago, Ill.), which debuted in January. (see BioCentury, Feb. 22, 2010 & Jan. 7, 2013).

Diaxonhit (Euronext:ALEHT), Paris, France Boehringer Ingelheim GmbH, Ingelheim, Germany Business: Cancer Boehringer Ingelheim partnered with Diazonhit to discover and characterize splice variants with Diaxonhit’s SpliceArray discovery platform that have the potential to be therapeutic cancer targets. Boehringer Ingelheim has an option to acquire rights to research, develop and commercialize any targets identified under the deal. The partners did not disclose financial terms.

Eddingpharm Inc., Shanghai, China Syndax Pharmaceuticals Inc., Waltham, Mass. Business: Cancer Eddingpharm received exclusive rights to develop and commercialize Syndax’s entinostat in China, Thailand, Taiwan and Malaysia. Syndax is eligible for undisclosed milestones and royalties. Eddingpharm can participate in the first three global Phase III registration trials of entinostat for any indication that would satisfy the China Food and Drug Administration (CFDA) requirements for approval in China. Eddingpharm will be responsible for all development costs in China. The companies will share all data. In I Q14, the ECOG-ACRIN Cancer Research Group plans to start a Phase III trial of the oral histone deacetylase (HDAC) inhibitor to treat estrogen receptor-positive breast cancer. Syndax will provide funding for the trial but said NIH’s National Cancer Institute will fund the “majority” of the trial. Syndax has exclusive, worldwide rights to entinostat from Bayer AG (Xetra:BAYN, Leverkusen, Germany).

See next page
Deals, from previous page

Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan
Business: Neurology

Eisai said it granted an undisclosed generics manufacturer non-exclusive U.S. commercialization rights to a generic version of the 23 mg tablet of Alzheimer’s disease (AD) drug Aricept donepezil. The manufacturer also received a non-exclusive license to Eisai IP covering the formulation. Eisai declined to disclose details. Aricept is a reversible acetylcholinesterase (AChE) inhibitor. According to a 10-Q filed by partner Pfizer Inc. (NYSE:PFE, New York, N.Y.) on Aug. 9, the Aricept 23 mg tablet lost U.S. exclusivity in July.

Galantos Pharma GmbH, Mainz, Germany

Neurodyn Inc., Charlottetown, Prince Edward Island
Business: Neurology

Neurodyn acquired lead Alzheimer’s candidate Memogain from Galantos for an undisclosed sum. Neurodyn said Memogain completed preclinical testing and plans to start Phase I testing late this year. Memogain is a prodrug of galantamine, an acetylcholinesterase (AChE) inhibitor and nicotinic receptor modulator. Neurodyn is reformulating or repurposing active biologic ingredients for neurological conditions. Neurodyn’s lead products include ND1208, a saponin-based biologic in preclinical testing for Parkinson’s disease; and ND602, which is based on the growth factor progranulin (PGRN; PCDGF) and is in preclinical testing for PD.

ImmunoGen Inc. (NASDAQ:IMGN), Waltham, Mass.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Business: Pharmaceuticals

ImmunoGen granted Eli Lilly exclusive rights to use ImmunoGen’s maytansinoid targeted antibody payload (TAP) technology to develop and commercialize products directed to an undisclosed antigen target. Immunogen will be eligible to receive up to $200.5 million in milestones, plus royalties. In 2011, ImmunoGen granted Eli Lilly rights to receive a limited number of exclusive licenses to use TAP with the pharma’s mAbs to develop antibody-drug conjugate (ADC) cancer therapeutics. The companies declined to provide details (see BioCentury, Jan. 2, 2012).

Interprotein Corp., Osaka, Japan
RaQualia Pharma Inc. (NASDAQ:4579), Aichi, Japan
Business: Neurology

Interprotein will receive an undisclosed milestone payment under a February deal to discover and develop protein-protein interaction inhibitors for undisclosed pain indications. The milestone was triggered by the assessments of inhibitors identified under the deal. The partners said 49 (18%) of 273 compounds tested were identified as hit compounds. The compounds were designed using Interprotein’s Engine for New Drug Design (INTENDD) technology and assessed by RaQualia. RaQualia is eligible for worldwide, exclusive rights of any products resulting from the partnership. Interprotein said it expects lead generation “in the near future.” RaQualia declined to disclose details (see BioCentury, Feb. 4).

Mimetica Pty. Ltd., Milton, Australia
Telesso Technologies Ltd., Sydney, Australia
Business: Dermatology

Telesso will acquire Mimetica in a stock deal that values Mimetica at A$16 million ($14 million). Telesso will issue 63 million shares to Mimetica shareholders at A$0.25 per share, plus 3 million options at A$0.11 per option. The options are exercisable at A$0.25 per share for a period of five years. In connection with the acquisition, Telesso plans to raise A$6.3 million ($5.8 million) through the sale of 26 million shares at A$0.25 per share, giving the company a market cap of A$24.5 million ($22 million). The offer is not underwritten.

Telesso plans to use the funds for a double-blind, U.S. Phase II trial to evaluate Mimetica’s MTC896 in 240 patients with moderate to severe acne. MTC896 is a small molecule inhibitor of melanocortin 5 receptor (MC5R). Under the proposed timeline, the trial would begin in 2Q14 and complete in 2Q15.

Telesso expects to close the acquisition by Oct. 11, after which Telesso will change its name to Mimetica Ltd., subject to shareholder approval. Telesso expects to relist on the ASX exchange under the ticker “TEO” on about Oct. 15, if all conditions are met. Telesso’s shares were suspended from trading on the ASX in December 2012 at the company’s request.

In 2008, Telesso closed its research facility and sold its core supercritical fluid technology to Map Pharmaceuticals Inc., which Allergan Inc. (NYSE:AGN, Irvine, Calif.) acquired in March. Since then, Telesso has searched for investment opportunities.

Opko Health Inc. (NYSE:OPK; Tel Aviv:OPK), Miami, Fla.

Prolor Biotech Inc., Ness Ziona, Israel
Business: Endocrine/Metabolic, Hematology

Opko Health completed the acquisition of Prolor Biotech. Prolor shareholders received 0.9951 Opko shares for every Prolor share held (see BioCentury, April 29).

Panacea Biotech Ltd., New Delhi, India
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Business: Infectious

Novartis said it and Panacea decided to amicably dissolve the 50-50 Indian JV Panacea Vaccines Pte. Ltd. for “strategic reasons.” The JV was formed in 2004 to develop next-generative combination vaccines for infectious diseases. Novartis, which acquired Chiron Corp. in 2006, declined to disclose details. Panacea could not be reached.

Pzena Inc. (NASDAQ:POZN), Chapel Hill, N.C.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Business: Cardiovascular

Sanofi granted Pzena U.S. rights to aspirin/omepazolone combinations PA32540 and PA8140, for $15 million up front and up to $20 million in pre-commercial milestones, plus undisclosed milestones and royalties. A combined NDA for the products is under FDA review for the secondary prevention of cardiovascular disease in patients at risk for aspirin-induced gastric ulcers with a Jan. 24, 2014, PDUFA date. Pzena will remain responsible for obtaining approval of the NDA, which will be transferred to Sanofi. Sanofi will be responsible for commercialization and future development of the products in the U.S. The parties will share costs for development activities required to obtain or maintain U.S. regulatory approval up to an undisclosed limit. The products are tablets comprising low- or high-dose aspirin and an immediate-release coating of 40 mg omeprazole, a proton pump inhibitor (PPI). PA32540 contains 325 mg aspirin and PA8140 contains 81 mg aspirin (see BioCentury, April 1).

Repligen Corp. (NASDAQ:RGEN), Waltham, Mass.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Business: Neurology

Repligen received a $1 million milestone payment from Pfizer under a 2012 deal granting the pharma exclusive, worldwide rights to develop and commercialize Repligen’s spinal muscular atrophy (SMA) program. The milestone, which is the first under the deal, was triggered by Repligen...
Deals, from previous page

completing technology transition obligations and completing the first two cohorts in a Phase I trial evaluating RG3039 in healthy volunteers.

Repligen is eligible for $64 million in remaining milestones, plus royalties. The deal includes Repligen’s undisclosed backup SMA compounds and lead compound RG3039, a small molecule inhibitor of decapping enzyme scavenger (DCPS). Repligen originally licensed rights to RG3039 in 2009 from the not-for-profit Families of Spinal Muscular Atrophy (see BioCentury, Jan. 7).

Santhera Pharmaceuticals Holding AG (SIX:SANN), Liestal, Switzerland

Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
Business: Neurology, Musculoskeletal

Santhera said it regained from Takeda exclusive, European and Swiss marketing rights to Catena idebenone for Duchenne muscular dystrophy (DMD), which Santhera granted Takeda in a 2007 deal. The companies also terminated a 2005 deal granting Takeda exclusive, EU and Swiss marketing rights to Catena to treat Friedreich’s ataxia (FRDA). Santhera said it approached Takeda to license back the rights “to increase strategic flexibility” after having discussions with third parties who were interested in obtaining worldwide marketing rights to the ubiquinone analog.

Takeda is now eligible to receive a percentage of future income up to €7 million ($9.3 million) generated by Santhera in DMD. Takeda is also eligible to receive €1 million ($1.3 million) as a percentage of Santhera’s future income in exchange for terminating the FRDA deal.

Santhera expects data in 2Q14 from the Phase III DELOS trial with Catena in DMD. Earlier this year, Santhera voluntarily withdrew Catena for FRDA from the Canadian market after Health Canada determined that additional clinical data did not confirm the product’s effectiveness. Santhera said it has no further plans for the product in FRDA. The company plans to resubmit an MAA to EMA early next year for idebenone under the name RXaxone to treat Leber’s hereditary optic neuropathy (LHON). Santhera withdrew the MAA in March.

The National Institutes of Health is also conducting a Phase II trial with idebenone to treat primary progressive multiple sclerosis (MS). Santhera has the rights to the results under a clinical trial agreement with NIH (see BioCentury, March 4 & June 17).

Ultragenyx Pharmaceutical Inc., Novato, Calif.

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

Kyowa partnered with Ultragenyx to co-develop and co-commercialize KRN23, which is in development for X-linked hypophosphatemia (XLH). Ultragenyx will lead development for KRN23 and the partners will share costs in the U.S., Canada and EU. The companies will co-commercialize KRN23 in the U.S. and Canada, and Kyowa will commercialize the compound in the EU. Ultragenyx will be solely responsible for development and commercialization in Mexico and Central and South America, and Kyowa will retain rights to KRN23 elsewhere. The companies declined to provide financial details.

KRN23, a human mAb against fibroblast growth factor 23 (FGF23), is in Phase II/III testing in the U.S. and Canada in adults, with a pediatric program slated to start next year. XLH is a rare metabolic bone disorder that is a heritable form of rickets.

Wilex AG (Xetra:WL6), Munich, Germany

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

Wilex’s Heidelberg Pharma GmbH subsidiary will use its antibody-drug conjugate (ADC) technology with undisclosed antibodies from Roche to develop antibody-targeted amanitin conjugates (ATACs) for cancer indications. Heidelberg’s ADC technology couples antibodies to alpha-amanitin, a bicyclic peptide that is found in the Amanita phalloides mushroom and inhibits RNA polymerase. The company said ATACs have shown activity against tumor cells independent of cell proliferation. Heidelberg will receive undisclosed “regular payments” for granting access to its technology and providing research services. Roche will have the exclusive option to license worldwide rights to develop and commercialize the compounds. Heidelberg would be eligible for undisclosed upfront payments plus milestones and royalties for each compound selected by Roche.

SALES & MARKETING

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

Becton’s BD Diagnostics unit launched its BD Max StaphSR Assay in Europe to detect Staphylococcus aureus and methicillin-resistant S. aureus (MRSA). The assay, which has CE Mark approval, identifies S. aureus and MRSA from nasal swabs in surgical patients at risk for colonization and runs on the BD Max system. The in vitro diagnostic detects the mec right-extremity junction (MREJ) that is found only in MRSA along with the mecA and mecC genes.

Biotronik SE & Co. KG, Berlin, Germany
Business: Cardiovascular

Biotronik launched 35 and 40 mm versions of its Orsiro Hybrid Drug-Eluting Stent in countries that recognize CE Mark approval to treat coronary artery stenosis. The product is a BiOblute-coated stent using a limus drug delivered by a bioabsorbable matrix. The company could not be reached for details.

Chugai Pharmaceutical Co. Ltd. (Tokyo:4519), Tokyo, Japan

Taisho Pharmaceutical Co. Ltd. (Tokyo:4535), Tokyo, Japan
Business: Musculoskeletal

Chugai and Taisho launched monthly IV Bonviva ibandronate in Japan to treat osteoporosis. The product has a Japanese National Health Insurance (NHI) list price of ¥4,918 ($49.92) per 1 mg syringe, the recommended monthly dose. Chugai partnered with Taisho in 2006 to co-develop and co-market in Japan the bisphosphonate that inhibits osteoclast-mediated bone resorption. The partners are developing a monthly oral formulation, which is in Phase III testing. Chugai is majority owned by Roche (SIX:ROG; OTCQX:RHHBY, Basel, Switzerland) (see BioCentury, Sept. 18, 2006).

Roche markets oral and IV formulations of ibandronate as Bonviva to treat osteoporosis in postmenopausal women, and an oral formulation to prevent osteoporosis in postmenopausal women. The product is marketed as Boniva in the U.S. GlaxoSmithKline plc (LSE:GSK; NYSE:GSK, London, U.K.) markets the product as Boniva in eastern European countries, while Nycomed, which Takeda Pharmaceutical Co. Ltd. (Tokyo:4502, Osaka, Japan) acquired, markets it in Asia-Pacific countries.

FSC Laboratories Inc., Charlotte, N.C.

Tris Pharma Inc., Monmouth Junction, N.J.
Business: Inflammation

Tris granted FSC exclusive commercialization rights to Korbinal ER carbinoxamine maleate oral suspension in the U.S. In April, FDA approved the oral antihistamine formulated with Tris’ OralXR+ technology to treat seasonal and perennial allergic rhinitis in children at least two years of age. Tris is eligible for up to $20 million in fixed and sales-related milestones, plus “significant” See next page
The companies are conducting a joint project under a €779,493 ($1 million) grant from the Eureka Eurostars program to develop NuQ biomarkers of early inflammation and transplant rejection responses. Specifically, the project seeks to identify biomarkers of graft-versus-host disease (GVHD) following hematopoietic stem cell transplantation. VolitionRx will lead the consortium and use its Nucleosomics biomarker development platform, which identifies and measures nucleosome structures in cell culture, serum, plasma or other biofluids. Discovery service provider Alcyomics will provide its Skinome human in vitro skin explant assay, which uses whole blood and tissue to identify adverse reactions to compounds not identified by animal testing. VolitionRx said it will be reimbursed about €420,000 ($554,778) over two years, or about 80% of its costs for the joint project.

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

Business: Neurology

Avanir and Actavis settled a 2011 suit alleging Actavis’ ANDA for a generic version of Nuedexta dextromethorphan/quinidine to treat pseudobulbar affect (PBA) infringes Avanir’s U.S. Patent Nos. 7,659,282 and RE38,115. Under the settlement, Actavis received rights to begin selling its generic version on July 30, 2026, or earlier under undisclosed criteria. PBA is characterized by involuntary episodes of laughing and/or crying.

The ‘282 patent, which expires in 2026, covers compositions comprising of dextromethorphan in combination with quinidine for treatment of neurological disorders. The ‘115 patent, which expires in 2016, covers the use of dextromethorphan with quinidine for treating intractable conditions.

Nuedexta is a combination of the NMDA receptor antagonist dextromethorphan with quinidine sulfate, a cytochrome P450 2D6 enzyme inhibitor. Avanir reported net sales of $19 million for Nuedexta for the fiscal 3Q13 ending June 30 (see BioCentury, Aug. 22, 2011).

Bayer AG (Xetra:BAY), Leverkusen, Germany

Business: Infectious

Bayer paid $74 million into a fund to settle a class action lawsuit that alleged Bayer violated antitrust and consumer protection laws related to sales of antimicrobial fluoroquinolone drug Cipro ciprofloxacin in California. The fund will compensate members of the class action suit, including consumers and third party payors who paid or reimbursed for Cipro in California between Jan. 8, 1997, and Oct. 31, 2004.

The plaintiffs filed the suit in 2002 in the Superior Court of the State of California claiming that Bayer and several generic manufacturers’ joint settlement agreement concerning patent litigation for Cipro violated California’s antitrust laws. The plaintiffs argue that the defendants agreed not to compete with each other, and thus kept lower-cost generic versions of Cipro off the market. According to the plaintiffs’ attorneys, the defendants deny the claims and say their conduct was legal. Bayer’s patent protection for Cipro expired in 2003. The plaintiffs argue that the defendants’ patent infringement occurred during the time Bayer was charging double-digit royalties. Tris will manufacture Karbinal ER. Tris said it expects the drug to be available in pharmacies “in time for the 2014 spring allergy season.”

MDxHealth S.A. (Euronext:MDXH), Liege, Belgium

Business: Diagnostic

MDxHealth said U.S. healthcare PPO network provider Stratose will cover MDxHealth’s ConfirmMDx for Prostate Cancer test. MDxHealth said the agreement adds 12.4 million covered lives for the test, and with MDxHealth’s existing payer agreements brings the total covered lives to over 80 million. The epigenetic laboratory-developed test (LDT) assesses the presence or absence of cancer cells in biopsy tissue, ruling out healthy men from undergoing unnecessary repeat biopsies. MDxHealth performs the test at its CLIA-certified laboratory or its co-marketing partner Plus Diagnostics (Union, N.J.) performs the test. In July, MDxHealth said the New York State Department of Health approved ConfirmMDx for Prostate Cancer test, allowing the company to offer the test in all U.S. states (see BioCentury, July 15).

Octapharma AG, Lachen, Switzerland

Business: Hematology

Octapharma launched Octaplus in the U.S. to manage preoperative or bleeding patients who require replacement of multiple plasma coagulation factors and to substitute intentionally removed plasma. FDA approved a BLA for Octaplus in January. Octaplus is a solution for infusion containing human plasma proteins (see BioCentury, Jan. 21).

Shionogi & Co. Ltd. (Tokyo:4507; Osaka:4507), Osaka, Japan

Business: Cardiovascular

Shionogi launched once-daily, oral Irtra irbesartan/trichloromethiazide in Japan to treat hypertension. The low dose tablet contains 100 mg irbesartan and 1 mg trichloromethiazide and the high dose tablet contains 200 mg irbesartan and 1 mg trichloromethiazide. The product has a Japanese National Health Insurance (NHI) price of ¥130.5 ($1.32) per low dose tablet and ¥195.8 ($1.99) per high dose tablet.

The product is a combination of irbesartan, an angiotensin II type I (AT1) receptor (AGTR1) antagonist, and the generic diuretic trichloromethiazide. Shionogi has development and commercialization rights from Sanofi (Euronext:SAN; NYSE:SNY, Paris, France) to irbesartan and 1 mg trichloromethiazide and the high dose tablet contains 200 mg irbesartan and 1 mg trichloromethiazide. The product has a Japanese National Health Insurance (NHI) price of ¥130.5 ($1.32) per low dose tablet and ¥195.8 ($1.99) per high dose tablet.

The product is a combination of irbesartan, an angiotensin II type

Spectrum Pharmaceuticals Inc. (NASDAQ:SPPI), Henderson, Nev.

Business: Cancer

Spectrum launched Marqibo vincristine in the U.S. to treat Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL) in patients with at least two relapses or in patients whose cancer has progressed following at least two leukemia therapies. The wholesale acquisition cost (WAC) of the nanoparticle liposomal formulation of vincristine is $9,750 for a 0.16 mg/mL dose given once weekly. The recommended dose is 2.25 mg/m² administered over one hour. Spectrum gained the product through its July acquisition of Talon Therapeutics Inc., which had exclusive, worldwide rights to Marqibo from Tekmira Pharmaceuticals Corp. (TSX:TKM;NASDAQ:TKMR, Burnaby, B.C.) under a 2006 deal (see BioCentury, July 22).

OTHER NEWS

Alcyomics Ltd., Gosforth, U.K.

VolitionRx Ltd. (OTCBB:VNRX), Singapore

Business: Inflammation

The institute launched the GARFIELD venous thromboembolism (VTE) registry to follow 10,000 patients with acute VTE who are indicated for anticoagulation. The registry will follow patients from 20-
Other News, from previous page

25 countries over four years and will focus on treatment duration, incidence of complications, practical aspects and health economic and outcomes research.

GARFIELD VTE is one of two registries in the GARFIELD outcomes research initiative led by the institute. The other program, GARFIELD AF, is following 50,000 newly diagnosed atrial fibrillation (AF) patients from 34 countries who are at risk of stroke. The institute said results to date from GARFIELD AF show anticoagulant therapy — particularly vitamin K antagonists — are underutilized in AF patients who are at high risk of stroke while being overused in low risk patients. Bayer’s Bayer HealthCare LLC subsidiary is supporting the GARFIELD initiative with an unrestricted research grant.

Bionovo Inc. (Pink:BNVIQ), Emeryville, Calif.

Business: Endocrine/Metabolic, Cancer

Bionovo partnered with IP Shakti to sell the biotech’s patent estate for its three women’s health therapeutics: Menerba, Bezielle and Selea. Last November, Bionovo said it would liquidate all of its assets after filing for Chapter 7 bankruptcy in the U.S. Bankruptcy Court for the District Court for the Northern District of California. IP Shakti is an early stage fund that de-risks technologies by performing proof of concept (POC) studies. The company selects IP assets, negotiates licenses and creates mechanisms for commercialization. Bionovo could not be reached for details.

Menerba, an estrogen receptor beta selective agonist, was in Phase III testing to treat hot flashes in postmenopausal women, but the company could not secure funding for the trial. Bezielle is an aqueous extract from the herb Scutellaria Barbata D. Don of the Lamiaceae family that inhibits glycolysis. The product has completed a Phase I trial to treat metastatic breast cancer. Selea, a selective estrogen receptor beta agonist, has completed preclinical testing to treat vaginal atrophy associated with menopause.

In March 2012, Bionovo reduced headcount by over 90% to save cash while the remaining management said it would cease operations if sufficient funds are not received or if the company is not sold (see BioCentury, March 19, 2012).

Consumer Watchdog, Santa Monica, Calif.

Public Patent Foundation, New York, N.Y.

Wisconsin Alumni Research Foundation (WARF), Madison, Wis.

Business: Gene/Cell therapy

Consumer Watchdog and the Public Patent Foundation filed suit in July in the U.S. Court of Appeals for the Federal Circuit seeking to invalidate WARF’s U.S. Patent No. 7,029,913. The ‘913 patent, issued in April 2006, covers techniques for creating in vitro cell cultures of human embryonic stem cells (hESC) as developed by University of Wisconsin researcher James Thomson. Watchdog and the foundation assert the techniques are ineligible for a patent under Section 101 of the Patent Act, which defines the subject matter eligible for patenting as “any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof.” Watchdog and the foundation said the next step is for the court to schedule oral arguments, which will likely be in November, December or January. WARF declined to comment on the case.

In a July 2 brief, Watchdog and the foundation asserted the hESC lines “are not markedly different from naturally occurring hES cells.” WARF responded in an Aug. 14 brief that the cell culture is “non-naturally occurring” and that the patent covers not only the cells but also “encompasses the culture medium, nutrients, and other components that sustain these cells outside the body in a plastic culture dish.” In an Aug. 29 brief, Watchdog and the foundation maintained the hESC lines “are not markedly different from those in our bodies” and are thus ineligible for Section 101 patentability.

Watchdog first filed a request for a reexamination of the patent in 2006. The U.S. Patent and Trademark Office (PTO) granted the reexamination and initially rejected, then upheld the patent. Watchdog appealed the decision to the agency’s Board of Appeals and Interferences, which also upheld the patent. Watchdog then appealed to the Federal Circuit.

Cubist Pharmaceuticals Inc. (NASDAQ:CBST), Lexington, Mass.

Optimer Pharmaceuticals Inc. (NASDAQ:OPTR), San Diego, Calif.

Business: Infectious

Cubist disclosed in an Aug. 27 SEC filing that it expressed interest multiple times in acquiring partner Optimer prior to the companies’ July deal. According to the filing, Cubist CEO Michael Bonney sent Optimer CEO Pedro Lichtinger a letter in March 2012, stating Cubist’s interest in acquiring Optimer at $20 per share. Optimer’s board rejected the offer. In June 2012, Bonney orally expressed Cubist’s interest in acquiring Optimer at $25 per share. However, when Lichtinger indicated he was not personally supportive of the transaction, Bonney informed him that Cubist’s expression of interest was withdrawn.

In late summer of 2012, it “became apparent to Optimer that the growth of Dificid had slowed.” Optimer co-promotes Dificid fidaxomicin with Cubist in the U.S. to treat Clostridium difficile-associated diarrhea (CDAD). Optimer launched Dificid in the U.S. in July 2011 and in Canada in June 2012. In September 2012, Cubist formally withdrew its offer to acquire Optimer for $25 per share because the company thought Dificid’s long-term value could be reduced by Optimer’s contemplated patient access initiatives.

At a Feb. 26 meeting, Optimer’s board said it was exploring strategic alternatives to maximize stockholder value, including a potential sale of Optimer (see BioCentury, March 4). On July 30, Cubist announced it would acquire Optimer in a cash and contingent value right (CVR) deal worth up to $801 million. Optimer shareholders will receive $10.75 in cash, which Cubist and Optimer said values Optimer at about $535 million. Optimer shareholders also will receive a tradable CVR for a one-time payment worth up to $5 tied to sales of Dificid in the U.S. and Canada between July 1, 2013, and Dec. 31, 2015. The deal is expected to close this year.

The companies reported 2Q13 net Dificid sales of $19 million in the U.S. and Canada. Dificid is a macrocyclic narrow-spectrum antibiotic (see BioCentury, Aug. 5).

Enanta Pharmaceuticals Inc. (NASDAQ:ENTA), Watertown, Mass.

National Institutes of Health, Bethesda, Md.

Business: Infectious

NIH’s National Institute of Allergy and Infectious Disease (NIAID) will provide Enanta with an additional $9.2 million in funding after extending its 2011 contract with the company to develop broad spectrum bicyclolide antibiotics against priority pathogens for biodefense. Enanta said the term of the contract has been extended to Feb. 28, 2015, from March 30, 2014.

Enanta has received a total of $23.5 million under the contract, including an initial $14.3 million payment. The company is eligible for a total of $42.7 million if NIAID exercises its option to further extend the contract to Sept. 30, 2016 (see BioCentury, Oct. 17, 2011).

Enanta will use the additional funding for preclinical and Phase I testing of EDP-788, the company’s lead bicyclolide antibiotic candidate. NIAID is funding development of EDP-788 as a countermeasure against multiple bacteria such as anthrax, plague and tularemia. Enanta said IND-
enabling studies of the water-soluble prodrug of EDP-322 are ongoing. EDP-322 is a bicyclolide with activity against bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). The company expects to start clinical trials in 1H14.

**GenVec Inc.** (NASDAQ: GNVC), Gaithersburg, Md.  
**Business:** Other  
GenVec said its board withdrew a plan to dissolve the company and liquidate its assets as a result of increased confidence that milestones in its hearing loss program with Novartis AG (NYSE:NVS; SIX:NOVN, Basel, Switzerland) can be realized. Instead, the company will restructure operations to focus on maximizing the value of its technology and assets, including its partnership with Novartis to develop treatments for hearing loss.

GenVec announced the dissolution plan in May and said it pursued several opportunities for dissolution that were ultimately not appropriate for lack of sufficient funding or inadequate recognition of the company’s value. GenVec believes shareholders are best served by preserving the hearing loss program, which will allow it the time necessary to find partners who assign a reasonable value to GenVec’s assets (see *BioCentury, June 10*).

In connection with the restructuring, Cynthia Collins departed as president and CEO and resigned as a director. CFO and SVP Douglas Swirsky replaced Collins as president and CEO and has become a director. Not including potential milestone payments from Novartis, GenVec said it has cash to fund operations through at least the end of 2014. At June 30, GenVec had $9.3 million in cash and a six-month operating loss of $6.2 million.

On June 28, GenVec said it had reduced headcount by 30 (73%) to 11. In its 2Q13 earnings, the company said due to the company’s efforts to terminate or further curtail a significant portion of its operations, it was no longer supporting much of its development programs.

In its 4Q12 earnings, GenVec announced it extended by one year through January 2014 a 2010 deal granting Novartis exclusive, worldwide rights to GenVec’s preclinical hearing loss and balance disorders program. Novartis is funding research for the preclinical program, which uses GenVec’s adenovector technology to delivery atonal homolog I (ATOH1; HATH1) to the inner ear. GenVec had received $600,000 in milestones under the deal and is eligible for up to an additional $206 million in remaining milestones, plus royalties (see *BioCentury, Jan. 25, 2010; Feb. 6, 2012 & April 29, 2013*).

**GlobalInnate Inc.,** Louisville, Colo.  
**Business:** Infectious  
GlobalInnate received a $4 million Research Project Grant (R01) from NIH’s National Institute of Allergy and Infectious Diseases (NIAID) to develop GlobalInnate’s Tarmogen products. The products are whole, heat-killed, recombinant *Saccharomyces cerevisiae* genetically modified to express a disease-associated antigen. The funding will be used to develop those products with the potential to prevent drug resistant forms of tuberculosis in the pre- and post-exposure setting, as well as to treat active tuberculosis infection.

**H. Lundbeck A/S (CSE:LUN),** Copenhagen, Denmark  
**Business:** Neurology  
H. Lundbeck filed an appeal in the EU General Court of a June 19 decision from the European Commission to fine Lundbeck 93.8 million (€124 million) for anticompetitive activity related to Lundbeck’s antidepressant Citalopram. The commission ruled that Lundbeck’s deals with four generic companies for the selective serotonin reuptake inhibitor (SSRI) violated competition law.

Lundbeck said the decision "contains several serious legal and factual errors,” including “misinterpreting the main criterion to determine whether an agreement restricts potential competition as established in case law and ignores key facts of the case.” The company also said the commission erred by imposing a fine “despite the novelty of the factual and legal issues raised in this case.” Lundbeck, which is asking the court to annul the EC’s decision and/or reduce the fine, expects a decision on the appeal within two to three years. The company said it is still obligated to pay the fine and will do so this quarter (see *BioCentury, June 24*).

**iPierian Inc.,** South San Francisco, Calif.  
**True North Therapeutics Inc.,** South San Francisco, Calif.  
**Business:** Hematology, Renal, Neurology  
iPierian spun out newco True North to develop iPierian’s TNT009, a mAb inhibitor of an undisclosed target in the complement pathway. TNT009 is in preclinical development to treat complement-mediated rare diseases in hematologic, renal and neurologic areas. iPierian CEO Nancy Stagliano will also be CEO of True North.

iPierian’s lead compound will now be IPN007, a mAb targeting microtubule-associated protein tau (MAPT; tau; FTDP-17) that is in preclinical development for Alzheimer’s disease (AD), with an IND submission slated for next year. iPierian said an IND submission for TNT009 is expected within 18 months.

**Isis Pharmaceuticals Inc.** (NASDAQ:ISIS), Carlsbad, Calif.  
**Gilead Sciences Inc.** (NASDAQ:GILD), Foster City, Calif.  
**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.  
**Business:** Infectious  
Gilead filed suit against Merck and Isis in the U.S. District Court for the Northern District of California seeking declaratory judgment that Gilead’s sofosbuvir does not infringe U.S. Patent Nos. 7,105,499 and 8,481,712. Merck and Isis are both listed as assignees on the two patents, which cover nucleoside analog inhibitors of RNA viral polymerase. Sofosbuvir, a single isomer form of a nucleotide analog HCV NS5B polymerase inhibitor, is under review in the U.S. to treat chronic HCV infection.

According to Gilead’s complaint, Merck sent a letter on Aug. 5 stating that Gilead would need to license rights to the ‘499 and ‘712 patent to commercialize sofosbuvir and pay Merck 10% royalty on net sofosbuvir sales until the patents expire. Gilead said it believes Merck’s demand is prohibitive and is meant to threaten Gilead with the prospect of a patent infringement suit “on the eve” of sofosbuvir’s Dec. 8 PDUFA date. Gilead noted that if approved, sofosbuvir will directly compete with Merck’s HCV drug Victrelis boceprevir. Merck recorded $226 million in 1H13 sales of Victrelis, a small molecule HCV NS3/4A protease inhibitor.

Sofosbuvir is also under accelerated assessment in the EU to treat chronic HCV infection. The compound has Fast Track designation in the U.S. for the indication.

According to Gilead’s complaint, Merck sent a letter on Aug. 5 stating that Gilead would need to license rights to the ‘499 and ‘712 patent to commercialize sofosbuvir and pay Merck 10% royalty on net sofosbuvir sales until the patents expire. Gilead said it believes Merck’s demand is prohibitive and is meant to threaten Gilead with the prospect of a patent infringement suit “on the eve” of sofosbuvir’s Dec. 8 PDUFA date. Gilead noted that if approved, sofosbuvir will directly compete with Merck’s HCV drug Victrelis boceprevir. Merck recorded $226 million in 1H13 sales of Victrelis, a small molecule HCV NS3/4A protease inhibitor.

Sofosbuvir is also under accelerated assessment in the EU to treat chronic HCV infection. The compound has Fast Track designation in the U.S. for the indication.

**Med BioGene Inc.** (TSX-V:MBI), Vancouver, B.C.  
**Business:** Diagnostic  
Diagnostic company Med BioGene said four shareholders discontinued a petition against the company that was filed in June in the British Columbia Supreme Court. The petition made claims against the company relating to the adoption of the Advance Notice Policy by the board in advance of the May 17 annual general meeting; Med BioGene’s subsequent rejection of a notice of intention from Lain Weir-Jones — one of the petitioners — to nominate himself and another person as
other news, from previous page

SurModics said it will restructure its executive leadership and corporate functions and realign its workforce to “better position it for long-term growth.” The restructuring will eliminate 7 positions (6%) and reduce headcount to 115. SurModics would not disclose from where the cuts would come. SurModics said the goal was to direct resources towards areas of growth and that its growth initiatives may result in new hires. The company said the restructuring, which is expected to save $900,000 to $1.1 million annually, will allow SurModics to increase investments in its business. SurModics said it will provide details on its growth initiatives in its annual guidance, which is slated for release in November.

SurModics’ quality, regulatory and clinical affairs function and its medical device R&D function will now directly report to CEO Gary Maharaj. The two corporate functions previously reported to business segment leaders. VP of Finance and CFO Andy LaFrence will now oversee SurModics’ operations and information systems functions, in addition to his VP and CFO responsibilities.

At June 30, SurModics had $28.4 million in cash, and a nine-month operating gain from continuing operations of $13.2 million for the fiscal year ending Sept. 30, 2013.

In 2011, SurModics sold its pharmaceuticals assets to specialty chemicals company Evonik Industries AG (Xetra:EVK; OTCBB:EVKIF, Essen, Germany) to focus on two core business units. Its medical device unit includes hydrophilic coatings and device drug delivery technology offerings, and its in vitro diagnostics (IVD) unit offers IVD test kits and microarrays (see BioCentury, Nov. 7, 2011 & Dec. 5, 2011).

Worldwide Innovative Networking (WIN) Consortium, Villejuif, France

Business: Bioinformatics, Cancer

The consortium received a €3 million ($4 million) grant from the EU’s Framework Programme 7 (FP7) to support the ongoing WINther trial. In the trial, cancer patients will receive therapies chosen based on individual DNA, RNA and microRNA profiles. The trial will enroll about 200 patients with metastatic solid tumors resistant to the last line of treatment. The primary endpoint is progression-free survival (PFS). Results from the trial are expected in 2015. The trial is also supported by Pfizer Inc. (NYSE:PFE, New York, N.Y.) and the National Breast Cancer Foundation Inc. (Frisco, Texas).

The consortium — which includes academic institutions, biotech and pharma companies and patient organizations — was founded in 2010 by the Institut Gustav Roussey (Villejuif, France) and the M.D. Anderson Cancer Center (Houston, Texas) to seek ways to increase the efficacy of cancer treatments through personalized medicine. The consortium runs several projects, including its Biomarker Registry Project, which will create a database that catalogues unpublished biomarker investigations.

management tracks

boards of directors

Acacia Pharma Ltd., Cambridge, U.K.

Business: Gastrointestinal, Endocrine/Metabolic, Other

Appointed: Martin Edwards, senior partner at Novo A/S; and Alex Pasteur, VP of Europe at Fidelity Biosciences

Arsanis Inc., Vienna, Austria

Business: Antibodies

Appointed: Claudio Nessi, partner at NeoMed Management

iPierian Inc., South San Francisco, Calif.

Business: Neurology, Gene/Cell therapy

Appointed: Rajeev Dadoo, partner at SR One

Kymab Ltd., Cambridge, U.K.

Business: Antibodies

Appointed: David Chiswell, a director, as chairman, effective Sept. 16; he succeeds Andrew Sandham, who is stepping down as chairman and CEO

see next page
Boards of Directors, from previous page

Mind-NRG, Geneva, Switzerland
Business: Neurology
Appointed: Debora Dumont, head of health & care at LRM N.V.

Otonomy Inc., San Diego, Calif.
Business: Drug delivery, Infectious
Appointed: Chau Khuong, private equity partner at OrbiMed Advisors

True North Therapeutics Inc., South San Francisco, Calif.
Business: Hematology, Renal, Neurology
Appointed: Rajeev Dadoo, partner at SR One

Management

Biocartis S.A., Lausanne, Switzerland
Business: Diagnostic
Hired: Ulrik Cordes as chief commercial officer, formerly director of global sales and marketing of slides & specialty glass at Thermo Fisher Scientific Inc.

Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Business: Biopharmaceuticals
Hired: Alan Eisenberg as VP of federal government relations, formerly EVP for emerging companies and business development at the Biotechnology Industry Organization

Champions Oncology Inc. (OTCBB:CSBR), Baltimore, Md.
Business: Cancer
Hired: Jim McCorry as EVP and general manager of the translational oncology solutions business, formerly EVP of commercial operations at Accellent Inc.

Chembio Diagnostics Inc. (NASDAQ:CEMI), Medford, N.Y.
Business: Diagnostic
Retiring: Lawrence Siebert as president and CEO, effective May 11, 2014

CollabRx Inc. (NASDAQ:CLRX), San Francisco, Calif.
Business: Bioinformatics
Transitioned: George Lundberg to CMO, while remaining editor-in-chief and chair of the editorial advisory board

GenVec Inc. (NASDAQ:GNVC), Gaithersburg, Md.
Business: Cancer, Cardiovascular, Ophthalmic
Departed: Cynthia Collins as president, CEO and a director; she is replaced by SVP and CFO Douglas Swirsky, who also became a director

Immune Design Corp., Seattle, Wash.
Business: Infectious
Hired: Richard Kenney as CMO, formerly CMO of Crucell N.V., which Johnson & Johnson acquired; he succeeds CMO Rachel Humphrey

Immunomedics Inc. (NASDAQ:IMMU), Morris Plains, N.J.
Business: Autoimmune, Cancer, Antibodies
Hired: Peter Pfuederschuh as VP of finance and CFO, formerly CFO of Circuite Inc.; he replaces Gerard Gorman, who is retiring

Business: Cancer, Inflammation
Hired: David Roth as SVP of clinical development and regulatory affairs, a newly created position, formerly VP at Pfizer Inc.’s oncology unit

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Business: Pharmaceuticals
Hired: Lynn Pendergrass as worldwide chairman of consumer, effective Sept. 16, formerly SVP and general manager at Hewlett-Packard Co.; she replaces Jesse Wu, who becomes chairman of Johnson & Johnson China, a newly created position

Kymab Ltd., Cambridge, U.K.
Business: Antibodies
Hired: Christian Groendahl as CEO, effective Sept. 16, formerly CSO of Zealand Pharma A/S; he succeeds Andrew Sandham, who is stepping down as chairman and CEO

Merck KGaA (Xetra:MRK), Darmstadt, Germany
Business: Pharmaceuticals, Other
Resigning: James Hoynes as president and head of U.S. operations of Merck’s EMD Serono Inc. subsidiary, effective Sept. 30

Mirati Therapeutics Inc. (NASDAQ:MRTX), San Diego, Calif.
Business: Cancer, Infectious
Hired: Isan Chen as chief medical and development officer, formerly CMO of Aragon Pharmaceuticals Inc., which Johnson & Johnson acquired; he succeeds CMO Rachel Humphrey

Ocera Therapeutics Inc. (NASDAQ:OCRX), San Diego, Calif.
Business: Gastrointestinal, Hepatic, Neurology
Hired: Jeryl Hilleman as CFO, formerly CFO of Amyris Inc.; she replaces Dana McGowan

True North Therapeutics Inc., South San Francisco, Calif.
Business: Hematology, Renal, Neurology
Hired: Nancy Stagliano as CEO, while remaining CEO of iPierian Inc.

Verona Pharma plc (LSE:VRP), London, U.K.
Business: Inflammation, Pulmonary
Hired: Richard Bungay as CFO, formerly CFO of Chroma Therapeutics Ltd.; he succeeds Danny Lowe

Vivus Inc. (NASDAQ:VVUS), Mountain View, Calif.
Business: Endocrine/Metabolic, Genitourinary, Neurology
Hired: Seth Fischer as CEO and a director, formerly company group chairman of Johnson & Johnson and worldwide franchise chairman of Johnson & Johnson’s Cordis Corp. subsidiary; he replaces Anthony Zook, who resigned for health reasons

Zealand Pharma A/S (CSE:ZEAL), Glostrup, Denmark
Business: Endocrine/Metabolic, Cardiovascular, Gastrointestinal
Hired: Torsten Hoffman as EVP and CEO, effective Oct. 1, formerly head of discovery chemistry in the pharma research division at Roche
**Clinical activities and selected announcements for the week ended September 6.**

### REGULATORY

**ALK-Abello A/S** (CSE:ALK-B), Horsholm, Denmark
**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.
Product: Grass pollen Allergy Immunotherapy Tablet (AIT), (Grazax) (MK-7243)
Business: Inflammation

ALK-Abello said FDA’s Allergenic Products Advisory Committee will meet on Nov. 6 to discuss a BLA from partner Merck for grass Allergy Immunotherapy Tablet (AIT). Merck said it expects a decision on the application in 1Q14, but declined to disclose a PDUFA date. The pharma has exclusive rights to develop and commercialize the tablet-based sublingual allergen immunotherapy in North America from ALK-Abello under a 2007 deal. ALK-Abello markets grass AIT as Grazax in Europe.

**Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.
**Daiichi Sankyo Co. Ltd.** (Tokyo:4568; Osaka:4568), Tokyo, Japan
Product: Ranmark denosumab (Prolia, Xgeva) (AMG 162)
Business: Cancer

Daiichi submitted a regulatory application in Japan for Ranmark denosumab to treat giant cell tumor of the bone. Daiichi already markets Ranmark in Japan to treat bone complications stemming from multiple myeloma (MM) and bone metastases from solid tumors. Denosumab is also approved in Japan as Pralia to treat osteoporosis.

The human mAb targeting receptor activator of NF-kappa B ligand (RANKL) is approved as Xgeva in the U.S. to treat giant cell tumor of the bone. Xgeva is also approved in the EU and U.S. to prevent skeletal related events (SREs) in adults with bone metastases from solid tumors. Denosumab is also approved in the U.S. and EU as Prolia to treat osteoporosis in postmenopausal women and in the EU to treat bone loss associated with hormone ablation in men with prostate cancer. Prolia is also approved in the U.S. to increase bone mass in men with osteoporosis at high risk for fracture. Daiichi has Japanese rights to denosumab to treat postmenopausal osteoporosis and bone-metastatic cancers from Amgen.

**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.
Product: Caprelsa vandetanib (ZD6474)
Business: Cancer

Germany’s Federal Joint Committee (G-BA) said in a final benefit assessment that Caprelsa vandetanib from AstraZeneca has “marginal” additional benefit over best supportive care for aggressive, symptomatic medullary thyroid cancer (MTC) that is unresectable, locally advanced or metastatic — the drug’s approved indication. In a June preliminary assessment, Germany’s Institute for Quality and Efficiency in Healthcare (IQWiG) said Caprelsa provides “no additional benefit” over best supportive care because of “uncertainty” with adverse event data for the drug, which IQWiG said meant it “cannot be ruled out” that Caprelsa’s negative effects outweigh its benefits. AstraZeneca submitted additional adverse event data for Caprelsa and data on severity of pain after IQWiG’s assessment (see BioCentury, June 24).

Last September, G-BA issued an unfavorable benefit assessment for Caprelsa because AstraZeneca provided data from a broader patient population than the 1 for which the EGFR and VEGF receptor kinase inhibitor is approved. The pharma took advantage of temporary changes to G-BA’s assessment process allowing companies to immediately resubmit dossiers for drugs that were given a “no additional benefit” rating because data were deemed incomplete (see BioCentury, June 18, 2012 & Sept. 10, 2012).

**Bayer AG** (Xetra:BAYN), Leverkusen, Germany
Product: Stivarga regorafenib (fluoro-sorafenib) (BAY 73-4506)
Business: Cancer

Bayer submitted an MAA to EMA seeking to expand the label of Stivarga regorafenib to include treatment of gastrointestinal stromal tumors (GIST) in patients who have previously been treated with 2 tyrosine kinase inhibitors (TKIs). The European Commission approved Stivarga in August to treat metastatic colorectal cancer (mCRC). The dual acting signal transduction (DAST) inhibitor of multiple kinases is already approved in the U.S. to treat mCRC and locally advanced, unresectable or metastatic GIST, for which it has Orphan Drug status in the U.S. Stivarga is also approved in Japan to treat unresectable, advanced or recurrent colorectal cancer and is under Priority Review in Japan to treat unresectable or metastatic GIST (see BioCentury, March 4 & April 1).

Onyx Pharmaceuticals Inc. (NASDAQ:ONXX, South San Francisco, Calif.) has co-promotion rights in the U.S. and is eligible for a 20% royalty on worldwide sales. Amgen Inc. (NASDAQ:AMGN, Thousand Oaks, Calif.) is acquiring Onyx for about $10.4 billion in cash (see BioCentury, Sept. 2).

**Bristol-Myers Squibb Co.** (NYSE:BMY), New York, N.Y.
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Product: Ilaris canakinumab (ACZ885)
Business: Autoimmune

The European Commission approved a regulatory application to expand the label of Novartis’ Ilaris canakinumab to include treatment of active systemic juvenile idiopathic arthritis (SJIA) in patients ≥2 years of age who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. The product was approved for the indication by FDA in May (see BioCentury, May 13). Ilaris is approved in >60 countries, including the U.S. and those in the EU, to treat cryopyrin-associated periodic syndromes (CAPS). The human anti-IL-1 beta mAb is also approved in the EU to treat gouty arthritis (see BioCentury, March 4).

The product uses UtiMAb technology from Medarex Inc., a subsidiary of Bristol-Myers. Regeneron Pharmaceuticals Inc. (NASDAQ:REGN, Tarrytown, N.Y.) is eligible for tiered royalties of 4-15% on sales of Ilaris under a 2009 deal (see BioCentury, June 15, 2009).

**Celgene Corp.** (NASDAQ:CELG), Summit, N.J.
**Taiho Pharmaceutical Co. Ltd.**., Tokyo, Japan
Product: Abraxane nab-paclitaxel (ABI-007)
Business: Cancer

FDA approved an sNDA from Celgene to expand the label of Abraxane nab-paclitaxel to include first-line treatment of advanced pancreatic cancer in combination with gemcitabine. The label includes a claim of overall survival (OS) benefit for pancreatic cancer, triggering a $300 million milestone payment to holders of the Abraxis BioScience Inc. contingent value right (CVR). Celgene acquired Abraxis in 2010 for about $2.9 billion plus the CVR (see BioCentury, July 5, 2010).

Abraxane is already approved in the U.S. for first-line treatment of advanced non-small cell lung cancer (NSCLC), and in the U.S., EU and at least 12 other countries as second-line treatment of metastatic breast cancer. The albumin stabilized nanoparticle formulation of paclitaxel is...
also under review for pancreatic cancer in the EU (see BioCentury, May 27). Otsuka’s Taiho Pharmaceutical Co. Ltd subsidiary has rights to the product in Japan, where it is approved to treat breast cancer.

**Chelseia Therapeutics International Ltd.** (NASDAQ:CHTP), Charlotte, N.C.

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

**Product:** Northera droxidopa

**Business:** Cardiovascular

Chelsea said the new PDUFA date for a resubmitted NDA for Northera droxidopa to treat symptomatic neurogenic orthostatic hypotension (NOH) is Feb. 14, 2014, just over a month later than the Jan. 3 PDUFA date the agency had originally assigned. In July, Chelsea said FDA identified undisclosed technical deficiencies with the application, which the company said would delay the PDUFA date.

Northera, an orally available synthetic precursor of norepinephrine, has Fast Track and Orphan Drug designations to treat symptomatic NOH in the U.S. and Orphan Drug designation to treat orthostatic hypotension in Europe. Dainippon granted Chelsea rights to Northera in the U.S. and Orphan Drug designation to treat orthostatic hypotension in Europe. Dainippon also under review for pancreatic cancer in the EU (see BioCentury, May 27).

**CSL Ltd.** (ASX:CSL), Melbourne, Australia

**Product:** Hizentra human immune globulin (IgPro20)

**Business:** Hematology

CSL said FDA approved a 10 g vial size of Hizentra human immune globulin to treat primary immunodeficiency. CSL said the new size will be available in the U.S. in October. Hizentra is also available in 1, 2 and 4 g vials. CSL also markets the 20% formulation of subcutaneous IgG in Europe as replacement therapy in patients with primary or secondary immunodeficiencies.

**Endo Health Solutions Inc.** (NASDAQ:ENDP), Chadds Ford, Pa.

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

**Product:** Aveed (Nebido) testosterone

**Business:** Endocrine/Metabolic

FDA accepted for review a resubmitted NDA from Endo for Aveed testosterone to treat male hypogonadism. The PDUFA date is Feb. 28, 2014. In May, the company said FDA issued a complete response letter and requested that Aveed’s REMS include a medication guide and elements to assure safe use (ETASU) “to mitigate the risks and severe complications related to post-injection reactions” (see BioCentury, June 3). Endo has exclusive, U.S. rights to the long-acting depot preparation of testosterone undecanoate from Bayer, which markets the product outside the U.S. as Nebido.

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

**Halozyme Therapeutics Inc.** (NASDAQ:HALO), San Diego, Calif.

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

**Product:** Subcutaneous Herceptin trastuzumab

**Business:** Cancer

The European Commission approved a subcutaneous formulation of Herceptin trastuzumab from Roche to treat HER2-positive breast cancer. Roche said subcutaneous administration of the humanized mAb against epidermal growth factor receptor 2 (EGFR2; HER2; ErbB2; neu) is less invasive and takes 2-5 minutes instead of 30-90 minutes with the approved IV administration. Subcutaneous Herceptin is formulated using Enhance recombinant human hyaluronidase (rHuPH20) drug delivery technology from Halozyme. Roche’s Genentech Inc. unit markets IV Herceptin in the U.S., while Roche markets the drug elsewhere. Chugai, which is majority owned by Roche, markets Herceptin in Japan.

**Genetic Technologies Ltd.** (ASX:GTG; NASDAQ:GENE), Fitzroy, Australia

**Product:** BREVAGen

**Business:** Diagnostic

Genetic Technologies said the New York State Department of Health issued a clinical laboratory permit to allow the company to perform its BREVAGen genetic test to determine an individual’s risk of developing non-familial breast cancer. The test is now available in all 50 states. The breast cancer stratification test combines a DNA-based profile of breast cancer-associated SNPs with the patient’s clinical history. Genetic Technologies received CE Mark approval for BREVAGen last year (see BioCentury, Aug. 13, 2012).

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

**Product:** Tafinlar dabrafenib (GSK2118436)

**Business:** Cancer

The European Commission approved an MAA from GlaxoSmithKline for Tafinlar dabrafenib as monotherapy to treat adults with unresectable or metastatic melanoma with a BRAF V600 mutation. The oral BRAF protein kinase inhibitor is also approved in the U.S. as monotherapy to treat melanoma with BRAF V600E mutations as detected by an FDA-approved test. MAAs for Tafinlar in combination with GSK’s melanoma drug trametinib and for trametinib as monotherapy are also under review for melanoma in Europe. In July, GSK submitted a pair of sNDAs to expand the label for Tafinlar and trametinib, which is approved as monotherapy under the name Mekinist, to include their use in combination. GSK in-licensed Mekinist, a small molecule inhibitor of MAP kinase kinase 1 (MAP2K1; MEK1) and MEK2, from Japan Tobacco Inc. (Tokyo:2914; Osaka:2914, Tokyo, Japan).

**Hisamitsu Pharmaceutical Co. Inc.** (Tokyo:4530; Osaka:4530), Tosu, Japan

**Product:** Estrana Tape

**Business:** Endocrine/Metabolic

Hisamitsu said it submitted a public knowledge-based application to Japan’s Ministry of Health, Labor and Welfare (MHLW) to expand the label of Estrana Tape estradiol transdermal patch to include treatment of hypoestrogenism due to causes such as hypogonadism. The patch is already marketed in Japan to treat menopausal disorder, ovarian deficiency symptoms and postmenopausal osteoporosis. Hisamitsu said the ministry allowed for submission of the application based on an evaluation conducted by the Evaluation Committee on Unapproved or Off-Labeled Drugs with High Medical Needs. The committee evaluates the medical needs for pharmaceuticals and indications that are approved in the U.S. or Europe but not in Japan, as well to confirm the appropri-
Regulatory, from previous page

ateness of the public knowledge-based application and the feasibility of additional studies for the approval application. Public knowledge-based applications can be submitted without newly conducting clinical studies if efficacy and safety of the drug is regarded as “publically known.”

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Product: Siltuximab (CNTO 328)
Business: Cancer

Johnson & Johnson’s Janssen R&D LLC subsidiary submitted a BLA to FDA and an MAA to EMA for siltuximab to treat multicentric Castleman’s disease (MCD) in patients who are HIV- and human herpes virus-8 (HHV-8)-negative. J&J said EMA granted accelerated assessment for the MAA. The company also said it requested Priority Review from FDA. The chimeric mAb against IL-6 is in Phase II testing for the indication. Siltuximab also is in Phase II testing for multiple myeloma (MM) and has completed a Phase II trial for metastatic prostate cancer that did not respond to hormone therapy.

The product has Orphan Drug designation in the U.S. and EU for MCD, which is a rare type of Castleman’s disease—a B cell proliferative disorder that is not malignant but is nonetheless fatal because of systemic inflammation—that affects more than 1 group of lymph nodes in different anatomical areas.

Pharmaxis Ltd. (ASX:PXS; Pink:PXSLY), Frenchs Forest, Australia
Product: Bronchitol mannitol
Business: Pulmonary

Pharmaxis said it will scale back resources and investments dedicated to the launch of Bronchitol mannitol in France due to delays in reaching an agreement with French authorities on a reimbursed price for the cystic fibrosis (CF) drug. The company will reduce personnel and contractors working on Bronchitol in France to 1 from 6 by the end of the month. Pharmaxis will focus marketing resources on the growth of Bronchitol sales in the launched markets of Germany, the U.K., Denmark and Australia, as well as its launch in new European markets.

The formulation of mannitol in a dry powder inhaler system is approved in the EU to treat CF patients aged ≥18 years as an add-on therapy to best standard of care. In May, Pharmaxis said that based on an end-of-review meeting with FDA, the agency is requiring an additional 6-month pivotal trial of Bronchitol to gain approval (see BioCentury, June 3). In March, Pharmaxis received a complete response letter from FDA for an NDA for Bronchitol to improve pulmonary function in CF patients ≥6 years of age. According to the company, FDA said submitted data from 2 Phase III trials did not provide a favorable risk-benefit balance (see BioCentury, March 25). Bronchitol has Orphan Drug and Fast Track designation in the U.S. and Orphan Drug status in the EU and Australia.

Shire plc (LSE:SHP; NASDAQ:SHPG), Dublin, Ireland
Shionogi & Co. Ltd. (Tokyo:4507; Osaka:4507), Osaka, Japan
Product: Elvanse (Vyanse) lisdexamfetamine dimesylate (S-877489)
Business: Neurology

Germany’s Institute for Quality and Efficiency in Healthcare (IQWiG) said ADHD drug Elvanse lisdexamfetamine dimesylate from Shire has “no additional benefit” over Strattera atomoxetine from Eli Lilly and Co. (NYSE:LLY, Indianapolis, Ind.) in patients ≥6 years who failed treatment with methylphenidate—its approved indication. IQWiG said data submitted by the company were not “relevant” because neither Elvanse nor atomoxetine were given as part of multimodal ADHD therapy, which would have included psychological, pedagogical and social components. Comments are due Sept. 23, with a final assessment from Germany’s Federal Joint Committee (G-BA) expected in mid-November.

The prodrug of amphetamine is approved as Vyvanse in the U.S. to treat ADHD and as maintenance treatment of ADHD in patients ≥6 years (see BioCentury, May 13). The product is approved in Canada in patients ages ≥6 and in Brazil as Venvanse in patients ages 6-12 years. In 2011, Shire partnered with Shionogi to co-develop and co-commercialize the product in Japan (see BioCentury, Nov. 21, 2011).

Sosei Group Corp. (Tokyo:4565), Tokyo, Japan
 Vectura Group plc (LSE:VEC), Chippenham, U.K.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Product: Seebri Breezhaler glycopyrronium bromide (NVA237) (formerly AD 237)
Business: Pulmonary

Novartis said its Seebri Breezhaler glycopyrronium bromide 50 µg was listed on the formulary of the Ontario Public Drug Program, which provides prescription drug coverage for Ontario residents ≥65 years of age, on social assistance, or residing in special care homes and long-term care facilities. The drug is listed as a “General Benefit” on the formulary, which allows reimbursement without restrictions. The inhaled long-acting muscarinic antagonist (LAMA) is approved for long-term, once-daily maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD).

Novartis markets Seebri Breezhaler for COPD in Europe, Japan, Canada and Australia. The pharma has global rights to develop and commercialize glycopyrronium bromide from Vectura and Sosei under a 2005 deal (see BioCentury, April 18, 2005).

Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
Product: Vedolizumab (MLN0002)
Business: Autoimmune

FDA accepted and granted Priority Review to a BLA from Takeda for vedolizumab to treat moderately to severely active ulcerative colitis (UC). The pharma declined to disclose the PDUFA date, but said it expects a decision by Feb. 18, 2014, which is 8 months from the date Takeda submitted the BLA. The agency also is reviewing vedolizumab to treat Crohn’s disease under a standard review. Takeda, which submitted a single BLA to FDA in June, said the agency chose to review the indications under different timelines (see BioCentury, June 24). In March, Takeda submitted an MAA to EMA for vedolizumab for the indications. The compound is a humanized mAb against integrin alpha(4)beta(7) (see BioCentury, March 11).

Zealand Pharma A/S (CSE:ZEAL), Glostrup, Denmark
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Product: Liximab lixisenatide (ZP10, AVE0010)
Business: Endocrine/Metabolic

Germany’s Federal Joint Committee (G-BA) said in a final benefit assessment that Type II diabetes drug Lixymia lixisenatide from Sanofi has “no additional benefit” over comparators. The assessment is in line with a June preliminary assessment from Germany’s Institute for Quality and Efficiency in Healthcare (IQWiG). Drugs that do not have an additional benefit are added to the reference pricing system, which gives a similar base price to all comparable drugs. If there is no reference, the company negotiates a price no higher than that of the comparator (see BioCentury, June 24). Lixymia, a glucagon-like peptide-1 receptor (GLP-1R) agonist, is under review in the U.S. with an undisclosed PDUFA date. Sanofi has global commercialization rights to the product from Zealand under a 2003 deal.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.

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

Product: Omecamtiv mecarbil (AMG 423) (formerly CK-1827452)

Business: Cardiovascular

Molecular target: Cardiac myosin

Description: Cardiac myosin activator

Indication: Treat patients with left ventricular systolic dysfunction hospitalized for acute heart failure

Endpoint: Dyspnea symptom response rate as measured by a 7-point Likert scale through 48 hours; Patient Global Assessment (PGA), change in N-terminal pro-brain natriuretic peptide (NT-proBNP), death or worsening heart failure within 7 days, days alive out of hospital up to day 30 and pharmacokinetics

Status: Phase IIb data

Milestone: Phase II data (1H14)

The double-blind, international Phase IIb ATOMIC-AHF trial in 613 patients with left ventricular systolic dysfunction hospitalized for acute heart failure showed that omecamtiv mecarbil given as a 48-hour IV infusion missed the primary endpoint of improving dyspnea symptom response rate as measured by a 7-point Likert scale vs. placebo (p=0.33). The trial protocol specified that the primary endpoint compare pooled data from all 3 omecamtiv mecarbil arms to pooled data from patients receiving placebo in the 3 cohorts. Patients received placebo or omecamtiv mecarbil to a target plasma concentration of 115, 230 or 310 ng/mL.

A supplemental analysis of the primary endpoint showed that high-dose omecamtiv mecarbil significantly improved dyspnea symptom response rate compared to the placebo arm for only the high-dose cohort (51% vs. 37%, p=0.03). Low- (42% vs. 41%) and mid-dose (47% vs. 46%) omecamtiv mecarbil did not significantly improve response rates compared to their individual placebo arms. Responders were defined as minimally, moderately or markedly better at 6 hours and moderately or markedly better at 24 and 48 hours without worsening heart failure or death for any cause by 48 hours.

On secondary endpoints, the incidence of worsening heart failure within 7 days of initiation of treatment with omecamtiv mecarbil was 13% for the low dose (p=0.179), 8% for the mid dose (p=0.034) and 9% for the high dose (p=0.075) compared to 17% for the pooled placebo group. There were 7 post-randomization myocardial infarctions (MI) in the omecamtiv mecarbil arms vs. 3 in the placebo arms. However, Amgen said there was no relationship between the maximum increase in baseline troponin levels and increasing plasma concentrations of omecamtiv mecarbil. The rates of adverse events, serious adverse events, adjudicated deaths and hospitalizations were similar between the treatment arms. Data were presented at the European Society of Cardiology meeting in Amsterdam.

Data from the Phase II COSMIC-HF trial evaluating an oral formulation of omecamtiv mecarbil in about 420 patients with chronic heart failure (CHF) and left ventricular systolic dysfunction are expected in 1H14. Amgen said that data from ATOMIC-AHF together with data from COSMIC-HF will inform its decision on whether to progress omecamtiv mecarbil into Phase III testing. Amgen has exclusive, worldwide rights to omecamtiv mecarbil from Cytokinetics (see BioCentury, June 1, 2009 & June 17, 2013).

Apitope International N.V., Diepenbeek, Belgium

Merck KGaA (Xetra:MRK), Darmstadt, Germany

Product: ATX-MS-1467

Business: Autoimmune

Molecular target: Major histocompatibility complex class I (MHC)

Description: Vaccine containing 4 synthetic peptides derived from human myelin basic protein

Indication: Treat relapsing multiple sclerosis (MS)

Endpoint: Safety; MRI evaluation for numbers of gadolinium-enhancing lesions and immunological activity

Status: Phase I data

Milestone: Start Phase II (early 2014); complete Phase II (2015)

An open-label, international Phase I trial in 43 patients with relapsing MS showed that 5 dose levels of intradermal ATX-MS-1467 every 2 weeks for 16 weeks led to a significant reduction in the number of contrast-enhancing brain lesions as measured by MRI. Apitope said “the same effect was not seen” in patients who received 5 dose levels of subcutaneous ATX-MS-1467. The company said the results allow Merck’s Merck Serono S.A. unit to develop plans for Phase II testing and beyond. Apitope said Phase II testing is slated to start early next year. Under a 2009 deal, Apitope is developing ATX-MS-1467 with Merck Serono, which is responsible for clinical trials starting from Phase II (see BioCentury, Jan. 19, 2009).

Arena Pharmaceuticals Inc. (NASDAQ:ARNA), San Diego, Calif.

Product: APD811

Business: Cardiovascular

Molecular target: Prostacyclin (IP) receptor (PGI2) (PTGIR)

Description: Prostacyclin (IP) receptor (PGI2) agonist

Indication: Treat pulmonary arterial hypertension (PAH)

Endpoint: Safety and pharmacokinetics

Status: Phase Ib data

Milestone: Start Phase II (1Q14)

A double-blind, placebo-controlled Phase Ib trial in 55 healthy volunteers showed that multiple ascending-doses of oral APD811 led to no serious adverse events. The most common treatment-emergent adverse events were headache, nausea and jaw pain. Arena previously reported data from a Phase I trial showing that single doses of APD811 were rapidly absorbed and showed dose-proportional pharmacokinetic exposure (see BioCentury, July 25, 2011).

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

Product: Lixiana edoxaban (DU-176b)

Business: Cardiovascular

Molecular target: Factor Xa

Description: Oral Factor Xa inhibitor

Indication: Treat and prevent recurrence of acute symptomatic venous thromboembolism (VTE) in patients with deep vein thrombosis (DVT) and/or pulmonary embolism (PE)

Endpoint: Recurrence of symptomatic VTE defined as a composite of recurrent symptomatic DVT, non-fatal symptomatic PE and fatal PE; composite of recurrent symptomatic DVT, non-fatal recurrent symptomatic PE and all-cause mortality, and clinically relevant major or non-major bleeding

Status: Phase III data

Milestone: Submit NDA (1Q14)

The double-blind, international Phase III Hokusai-VTE trial in 8,292 patients with acute symptomatic DVT, PE or both showed that once-daily edoxaban plus heparin met the primary endpoint of non-inferiority to warfarin plus heparin in reducing the incidence of recurrent symptomatic VTE (3.2% vs. 3.5%, p<0.001 for non-inferiority). On the primary safety endpoint, the rate of clinically relevant bleeding was significantly lower for edoxaban compared to warfarin (8.5% vs. 10.3%, p=0.004). In patients with DVT (n=4,921), VTE recurrence rates were
similar in the edoxaban and warfarin arms (3.4% vs. 3.3%, HR = 1.02, 95% CI: 0.75, 1.38). In patients with PE (n=3,319), the incidence of recurrent VTE was numerically lower in the edoxaban arm compared to the warfarin arm (2.8% vs. 3.9%, HR = 0.70, 95% CI: 0.5, 1.06).

In a subgroup analysis of patients with severe PE and evidence of right ventricular dysfunction (n=938), edoxaban led to a 48% lower risk of recurrent symptomatic VTE vs. warfarin (3.3% vs. 6.2%, HR=0.52, 95% CI: 0.28, 0.98). Patients received warfarin or once-daily 60 mg edoxaban (30 mg for patients with renal impairment, low body weight or concomitant use of certain P-glycoprotein inhibitors) for at least 3 months and up to a maximum of 1 year. Data were published in the New England Journal of Medicine and presented at the European Society of Cardiology meeting in Amsterdam.

By 1Q14, Daiichi plans to submit regulatory applications for edoxaban in VTE in the U.S., Europe and Japan. Edoxaban is also in the Phase III ENGAGE AF-TIMI trial to prevent stroke and systemic embolic events in patients with atrial fibrillation (AF). Data from ENGAGE AF-TIMI are slated to be presented at the American Heart Association meeting in Dallas in November. Edoxaban is approved as Lixiana in Japan to prevent VTE after major orthopedic surgery.

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

**Product:** NewMet

**Business:** Endocrine/Metabolic

**Molecular target:** NA

**Description:** Delayed-release formulation of metformin

**Indication:** Treat Type II diabetes

**Endpoint:** Change from baseline in fasting plasma glucose (FPG) at week 4; FPG at week 12, HbA1c, weight and safety

**Status:** Phase Ib/IIa data

**Milestone:** Additional Phase Ib/IIa data (10/2013)

Top-line data from a double-blind, dose-finding, U.S. Phase Ib/II trial in 240 Type II diabetics showed that once-daily oral NewMet met the primary endpoint of reducing FPG from baseline to week 4 vs. placebo. Patients are receiving placebo; once-daily 600, 800 or 1,000 mg NewMet; or once-daily 1,000 or 2,000 mg doses of a generic extended-release formulation of metformin. Elicelyx expects to report 12-week data in October. The company said the data confirm previous studies showing that NewMet reduced FPG to a similar extent as generic metformin but at plasma exposure levels previously shown to be as much as 65% lower than comparable doses of generic metformin. Elicelyx said the reduced systemic absorption of NewMet indicates that the product may be an appropriate treatment for Type II diabetics who have renal impairment and are contraindicated for metformin use due to the risk of lactic acidosis. The company is also conducting a pharmacokinetic study with NewMet in Type II diabetics with mild, moderate and severe renal impairment. Elicelyx said the Phase Ib/II and PK trials will conclude the Phase II program, after which the company plans to sell NewMet to a pharmacy company with a primary care sales force.

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

**Product:** LY2405319

**Business:** Endocrine/Metabolic

**Molecular target:** Fibroblast growth factor 21 (FGF21)

**Description:** Oral dipeptidyl peptidase-4 (DPP-4) inhibitor

**Indication:** Treat Type II diabetes

**Milestone:** Start Phase IIb (10/2013)

**Endpoint:** Safety and pharmacokinetics; percent change from baseline in LDL-C, other lipids and cardiometabolic risk factors

**Status:** Phase IIa data

Top-line data from the double-blind, U.S. Phase IIa ETC-1002-007 trial in 58 patients with hypercholesterolemia showed that once-daily oral ETC-1002 plus 10 mg atorvastatin led to a significant incremental LDL-C lowering of 22% from baseline to week 8 vs. 0% for placebo plus 10 mg atorvastatin (p<0.0001). ETC-1002 was well tolerated with no serious adverse events reported. Patients received placebo for 8 weeks or once-daily 60 mg ETC-1002 for the first 2 weeks followed by once-daily 120, 180 and 240 mg ETC-1002 for 2 weeks each.

In June, Esperion reported data from a separate Phase IIa trial in 56 patients with hypercholesterolemia and a history of intolerance to ≥2 statins showing that once-daily oral ETC-1002 met the primary endpoint of reducing mean LDL-C from baseline to week 8 vs. placebo (32% vs. 3%, p<0.0001) (see BioCentury, June 10). Next month, Esperion plans to start the Phase IIb ETC-1002-008 trial to evaluate ETC-1002 for 12 weeks vs. Zetia ezetimibe in patients with hypercholesterolemia. Merck & Co. Inc. (NYSE:MRK, Whitehouse Station, N.J.) markets Zetia and Pfizer Inc. (NYSE:PFZ; New York, N.Y.) markets Lipitor atorvastatin.

**Furiex Pharmaceuticals Inc. (NASDAQ:FURX), Morrisville, N.C.**

**Product:** Nesina alogliptin (SYR-322)

**Business:** Endocrine/Metabolic

**Molecular target:** Dipeptidyl peptidase-4 (DPP-4) (CD26)

**Description:** Oral dipeptidyl peptidase-4 (DPP-4) inhibitor

**Indication:** Treat Type II diabetes

**Milestone:** NA

**Endpoint:** Composite of cardiovascular (CV) death, non-fatal myocardial infarction and hospitalization for unstable angina

A double-blind, U.S. Phase I trial in 46 obese patients with Type II diabetes showed that once-daily subcutaneous LY2405319 significantly reduced LDL-C from baseline to week 4 by 29.5% at the 10 mg dose and 20.2% at the 20 mg dose vs. 0.75% for placebo (p<0.05 for both). LY2405319 also significantly reduced triglyceride levels from baseline to week 4 by 46.2% at the 10 mg dose and 44.6% at the 20 mg dose vs. an increase of 2.5% for placebo (p<0.05 for both). Additionally, LY2405319 significantly reduced total cholesterol from baseline to week 4 by 19.2% at the 10 mg dose and 15.4% at the 20 mg dose vs. 0.63% for placebo (p<0.05 for both). LY2405319 also significantly increased HDL-C from baseline to week 4 by 15.6% at the 3 mg dose, 15.2% at the 10 mg dose and 19.5% at the 20 mg dose vs. a reduction of 2.3% for placebo (p<0.05 for all). Furthermore, LY2405319 led to reductions in body weight at the mid- (1.75 kg) and high-dose (1.49 kg) at week 4 that were significant compared to baseline (p<0.05), but non-significant compared to placebo (0.229 kg). No dose of LY2405319 significantly improved fasting glucose or insulin levels from baseline to week 4 vs. placebo. There were 3 serious adverse events with LY2405319, including cholecystitis, optic neuropathy and a severe reaction characterized by a drop in blood pressure, urticaria and pruritis. Data were published in Cell Metabolism.
Clinical Results, from previous page

infarction (MI) and non-fatal stroke; composite of CV death, non-fatal MI, non-fatal stroke and urgent revascularization due to unstable angina

Status: Phase III data

Milestone: NA

The double-blind, international Phase III EXAMINE cardiovascular outcomes trial in 5,380 Type II diabetics with acute coronary syndrome (ACS) showed that once-daily oral alogliptin in combination with patients’ existing anti-hyperglycemic and cardiovascular therapy met the primary endpoint of non-inferiority to placebo plus existing therapy in the incidence of the composite of CV death, non-fatal MI or non-fatal stroke at a median follow-up of 18 months. Specifically, the primary composite endpoint occurred in 1.3% (n=305) of patients receiving alogliptin vs. 1.8% (n=316) of patients receiving placebo (HR=0.96, p<0.001 for non-inferiority). The pre-specified non-inferiority margin was a hazard ratio of 1.3. Alogliptin was not superior to placebo on the composite primary endpoint (p=0.32 for superiority).

Alogliptin was also non-inferior to placebo on the secondary composite endpoint of the incidence of CV death, non-fatal MI, non-fatal stroke or urgent revascularization due to unstable angina (12.7% vs. 13.4%, HR=0.95). Additionally, hazard ratios for death from any cause and CV death were consistent with the hazard ratio for the primary composite endpoint. Alogliptin also significantly reduced mean HbA1c from baseline to the end of treatment by 0.33% vs. an increase of 0.3% in the placebo group. The primary outcome analysis demonstrated a statistically significant decrease in the incidence of serious adverse events, an endpoint not prespecified in the protocol. The incidence of serious adverse events was 23.3% in the alogliptin group compared with 24.4% in the placebo group (HR=0.95, p=0.007). The most common adverse events were hypoglycemia and pancreatitis, which were similar between treatment groups.

The double-blind, international Phase III DERMA trial in 1,345 stage IIIA/C melanoma patients with macroscopic nodal disease whose tumors expressed the MAGEA3 gene showed that intramuscular MAGEA3 given after surgical removal of a patient’s tumors missed the coprimary endpoint of improving DFS vs. placebo. Patients received up to 13 injections of MAGEA3 over a period of 27 months. Based on the recommendation of an independent DMC, GlaxoSmithKline said that it will continue the trial until the second co-primary endpoint is assessed. The endpoint, DFS in a gene signature-positive subgroup, is designed to identify a subset of MAGEA3-positive patients that may benefit from treatment with MAGEA3. The subset data are expected in 2015. GSK said the data remain blinded and that it is still working to determine exactly how many gene signatures will be evaluated.

Data from the Phase III MAGRIT trial of MAGE-A3 to treat non-small cell lung cancer (NSCLC) following surgical removal of the primary tumor are expected in 1H14. The AS15 adjuvant is a liposomal formulation of the QS-21 Stimulon adjuvant from Agenus Inc. (NASDAQ:AGEN, Lexington, Mass.) in combination with monophosphoryl lipid A and CpG7909 (PF-3512676), a toll-like receptor 9 (TLR9) agonist that Pfizer Inc. (NYSE:PFE, New York, N.Y.) discontinued development of in 2010. GSK licensed rights to QS-21 Stimulon from Agenus in 2006 (see BioCentury, July 17, 2006). Last year, Agenus granted GSK the first right to negotiate for the purchase of Agenus or certain of its assets (see BioCentury, March 12, 2012).

Iroko Pharmaceuticals LLC, Philadelphia, Pa.

Product: Lower dose submicron diclofenac (Nanoformulated diclofenac)

Business: Neurology

Molecular target: NA

Description: Nanoformulation of the NSAID diclofenac using SoluMatrix nanof ormulation technology

Indication: Treat post-surgical acute pain

Endpoint: Visual Analog Scale Summed Pain Intensity Difference (VASSPID) over 48 hours; VAS pain intensity score at each time point up to 48 hours, time to first rescue medication and the proportion of patients using rescue medication

Status: Phase III data

Milestone: NA

A double-blind, U.S. Phase III trial in 428 patients undergoing bunionectomy under regional anesthesia showed that thrice-daily 18 and 35 mg submicron diclofenac each met the primary endpoint of reducing pain intensity as measured by VASSPID scores over 48 hours following surgery vs. placebo (p=0.011 and p<0.011, respectively). On secondary endpoints, a significantly smaller proportion of patients receiving low- and high-dose submicron diclofenac required opioid-containing rescue medication for pain vs. placebo (85% and 82%, respectively, vs. 97%, p=0.005 and p=0.002). In the active comparator arm, 85% of patients receiving celecoxib required opioid-containing rescue medication for pain (p=0.006). Additionally, patients receiving low- and high-dose submicron diclofenac were able to significantly delay time to use of opioid rescue medications vs. placebo (9.1 and 5.9 hour delays, respectively, vs. a 2.7 hour delay, p<0.001 for both). Celecoxib led to a 4.9 hour delay in time to use of opioid rescue medications vs. placebo (9.1 and 5.9 hour delays, respectively, vs. a 2.7 hour delay, p<0.001 for both). Celecoxib led to a 4.9 hour delay in time to use of opioid rescue medications vs. placebo (9.1 and 5.9 hour delays, respectively, vs. a 2.7 hour delay, p<0.001 for both).
Clinical Results, from previous page

not adequately relieved by study medication. Data were presented at the PAINWeek meeting in Las Vegas.

In February, FDA accepted for review an NDA for submicron diclofenac to treat mild to moderate acute pain in adults. The company declined to disclose the PDUFA date or the date it submitted the application. Data from the bunionection trial were included in the application (see BioCentury, March 11). Pfizer Inc. (NYSE:PFE, New York, N.Y.) markets celecoxib for osteoarthritis (OA) and rheumatoid arthritis (RA) in the EU as Onsenal and in the U.S. as Celebrex. The product is also approved in the U.S. to treat ankylosing spondylitis. Astellas Pharma Inc. (Tokyo:4503, Tokyo, Japan) has rights to the compound in Japan, where it is known as Celecox.

Jennex Biotherapeutics Inc., San Francisco, Calif.
Lee’s Pharmaceutical Holdings Ltd. (HKSE:0950), Hong Kong, China
Transgene S.A. (Euronext:TNG), Illkirch, France
Green Cross Corp. (KSE:006280), Yongin-Si, South Korea
Product: Pexa-Vect (pexastimogene devacirepvec) (JX-594, TG6006)
Business: Cancer
Molecular target: Granulocyte macrophage colony-stimulating factor (GM-CSF) (CSF2)
Description: Recombinant vaccinia virus (addition of GM-CSF and deletion of thymidine kinase)
Indication: Second-line treatment of advanced hepatocellular carcinoma (HCC)
Endpoint: Overall survival (OS); time to tumor progression, quality of life, tumor response, time to symptomatic progression and safety
Status: Phase IIb discontinued
Milestone: NA

Transgene stopped the open-label, international Phase IIb TRAVERSE trial after data from 80 patients with advanced HCC who have failed sorafenib showed that Pexa-Vect plus best supportive care (BSC) missed the primary endpoint of improving OS vs. BSC alone. The company said the pre-specified number of patients required for the OS analysis was >73. The trial planned to enroll about 126 patients. Pexa-Vect was generally well tolerated. Transgene said in 4Q13 it will determine whether to move Pexa-Vect into Phase III testing for first-line HCC, which would start next year. Pexa-Vect is also in a Phase Ila trial for patients with sorafenib-naïve HCC, a Phase Ila trial for treatment-refractory kidney cancer, a Phase I/II trial for treatment-refractory colorectal cancer and an exploratory trial for ovarian cancer. The product has Orphan Drug designation in the U.S. and Europe for HCC.

Transgene has exclusive rights from Jennex to develop and commercialize Pexa-Vect in Europe, the Commonwealth of Independent States and the Middle East, while Lee’s Pharmaceutical has exclusive rights in China. Green Cross has rights in South Korea. Bayer AG (Xetra:BAYN, Leverkusen, Germany) and Onyx Pharmaceuticals Inc. (NASDAQ:ONXX, South San Francisco, Calif.) market Nexavar sorafenib.

Medivir AB (SSE:MVIR B), Huddinge, Sweden
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Product: Simeprevir (TM435) (formerly TM435350)
Business: Infectious
Molecular target: HCV NS3/4A protease complex
Description: HCV NS3/4A protease inhibitor
Indication: Treat HCV genotype 1 infection
Endpoint: Proportion of patients with a sustained virologic response (SVR) 12 weeks after end of treatment; rapid virologic response (RVR) at week 4, end of treatment response, SVR4 and safety
Status: Additional Phase IIa data
Milestone: NA

Interim data from 41 evaluable treatment-naïve patients and previous null responders with HCV genotype 1 infection and advanced liver fibrosis (METAVIR scores of F3-F4) in cohort 2 of the open-label, U.S. Phase IIa COSMOS trial showed that once-daily 150 mg oral simeprevir plus once-daily 400 mg oral sofosbuvir (GS-7977) for 12 weeks led to an SVR 4 weeks after the end of treatment in 96% of patients when given with ribavirin (n=27) and in 100% of patients when given without ribavirin (n=14). In cohort 2, 78.2% of evaluable patients had HCV genotype 1a infection, 47.1% had a METAVIR score of F4 (cirrhosis) and 54% were null responders. The regimen of simeprevir plus sofosbuvir with or without ribavirin was generally well tolerated. Medivir previously reported SVR4 and SVR8 data from 80 null responders to peginterferon and ribavirin with HCV genotype 1 infection and mild to moderate liver fibrosis (METAVIR scores of F0-F2) in cohort 1 of the trial (see BioCentury, March 11). There were no viral breakthroughs in either cohort.

In May, FDA accepted and granted Priority Review to an NDA for simeprevir to treat HCV genotype 1 infection in adult patients with compensated liver disease. An 8-month Priority Review would place the PDUFA date in November; the specific date is not disclosed (see BioCentury, May 20). Simeprevir is also under review in the EU. Johnson & Johnson’s Janssen R&D Ireland has ex-Nordic rights to develop and commercialize simeprevir from Medivir. Simeprevir has Fast Track designation in the U.S.

In June, FDA accepted and granted Priority Review to an NDA from Gilead Sciences Inc. (NASDAQ:GILD, Foster City, Calif.) for sofosbuvir to treat chronic HCV infection. The PDUFA date is Dec. 8. The company said the application covers the use of sofosbuvir in combination with ribavirin as an all-oral therapy to treat HCV genotypes 2 and 3 infection; and sofosbuvir in combination with ribavirin and pegylated interferon to treat HCV genotypes 1, 4, 5 and 6 infection in treatment-naïve patients. The single isomer form of PSI-7851, a nucleotide analog HCV NS5B polymerase inhibitor, is also under accelerated assessment in the EU for the same indications. An accelerated assessment shortens the review period to 150 days from 210 (see BioCentury, May 27 & June 10). Sofosbuvir has Fast Track designation in the U.S. to treat chronic HCV infection.

In 2011, Gilead’s Pharmasset Inc. unit partnered with J&J to evaluate a combination of the companies’ HCV candidates in a Phase II trial. Roche (SIX:ROG; OTCQX:RHHBY, Basel, Switzerland) markets Pegasis peginterferon alfa-2a and Copegus ribavirin.

Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Product: Aliskiren (Rasilieze, Tekturna) (SPP100)
Business: Cardiovascular
Molecular target: Renin
Description: Renin inhibitor
Indication: Reduce progression of coronary atherosclerosis in patients with coronary artery disease (CAD) and pre-hypertension
Endpoint: Progression of coronary atherosclerosis as defined by the change from baseline in percent atheroma volume (PAV) after ≥72 weeks of treatment; total atheroma volume (TAV), proportion of patients showing regression of atheroma defined as any reduction in PAV of TAV from baseline, and safety
Status: Phase III data
Milestone: NA

Data from 458 evaluable patients in the double-blind, international Phase III AQUARIUS trial showed that once-daily 300 mg aliskiren given for ≥72 weeks missed the primary endpoint of reducing the progression of coronary atherosclerosis, defined by the change from baseline in PAV, vs. placebo. Specifically, aliskiren reduced PAV by 0.33% vs. a 0.11% increase for placebo (p=0.08). Aliskiren also missed the secondary
Clinical Results, from previous page

epoint of reducing TAV from baseline vs. placebo (4 vs. 2.1 mm3, p=0.18). Additionally, aliskiren non-significantly improved the proportion of patients with regression of PAV (56.9% vs. 48.9%, p=0.09) and TAV (64.4% vs. 57.5%, p=0.13) vs. placebo. PAV and TAV were measured using intravascular ultrasound (IVUS) and higher values correlate with disease progression.

A pre-specified exploratory analysis showed that aliskiren significantly reduced systolic (2.9 vs. 0.8 mmHg, p=0.007) and diastolic (2 vs. 0.4 mmHg, p=0.003) blood pressure from baseline vs. placebo. Additionally, patients in the aliskiren arm had a lower incidence of major cardiovascular events (8.5% vs. 16.2%, p=0.004) and non-fatal myocardial infarctions (0.3% vs. 2.6%, p=0.02) vs. placebo. However, the study authors said the trial was not powered to assess clinical outcomes and therefore the exploratory endpoint data should be considered hypothesis generating data that warrant further investigation. The trial enrolled 613 patients with CAD, pre-hypertensive blood pressure at baseline and 2 additional cardiovascular risk factors. Data were published in the Journal of the American Medical Association and presented at the European Society of Cardiology meeting in Amsterdam. Novartis markets aliskiren as Tekturna in the U.S. and as Rasilez in the EU to treat hypertension. The company also markets Tekamlo aliskiren/amlopipline in the U.S. for hypertension.

**Orexo AB** (SSE:ORX), Uppsala, Sweden

Product: OX51

Business: Neurology

Molecular target: NA

Description: Sublingual tablet formulation of alfentanil

Indication: Prevent procedure-induced pain

Endpoint: Worst pain intensity experienced during prostate biopsy measured immediately after the end of the biopsy procedure by a numerical rating scale (NRS); safety and pharmacokinetics

Status: Phase II data

Milestone: NA

The double-blind, dose-finding, placebo-controlled, European Phase II OX51-002 trial in 180 patients undergoing elective prostate biopsy showed that oral OX51 met the primary endpoint of analgesic efficacy by achieving a significant dose response in maximal pain experience during the biopsy procedure. Details were not disclosed. OX51 was well tolerated in all dose groups. Additionally, OX51 showed no effect on quantitative scales for assessment of sedation and drowsiness vs. placebo. Patients received placebo or 1 of 3 doses of OX51. Orexo said it plans to consult with regulatory authorities to determine the best path forward for OX51.

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

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

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

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

**Business**: Endocrine/Metabolic

**Molecular target**: Dipeptidyl peptidase-4 (DPP-4) (CD26)

**Description**: Oral dipeptidyl peptidase-4 (DPP-4) inhibitor

**Indication**: Treat Type II diabetes

**Endpoint**: Reduction of 0.6% in atheroma volume from baseline to week 12 (p<0.001 for non-inferiority) measured using intravascular ultrasound (IVUS); change in total atheroma volume, percent change in APOA1 and HDL-C and safety

**Status**: Additional Phase IV data

**Milestone**: NA

Additional data from the double-blind, international Phase IV SAVOR-TIMI 53 cardiovascular outcomes trials in 16,492 Type II diabetics showed that the primary efficacy endpoint of the incidence of the composite of CV death, non-fatal MI or non-fatal ischemic stroke occurred in 7.3% (n=613) of patients receiving once-daily Onglyza and 7.2% of patients (n=609) receiving placebo at a median follow-up of 2.1 years (HR=1, 95% CI: 0.89, 1.12, p=0.09 for superiority). Bristol-Myers previously reported that Onglyza missed the primary efficacy endpoint of superiority to placebo on the composite. Onglyza did meet the primary safety endpoint of non-inferiority to placebo on the composite (p<0.001 for non-inferiority) (see BioCentury, June 24). Bristol-Myers said the trial was designed in part to fulfill a postmarketing requirement requested by FDA to show an upper bound of the 2-sided 95% CI of <1.3 for the estimated risk ratio comparing Onglyza to placebo in the incidence of major adverse cardiac events.

Additionally, the secondary composite endpoint of CV death, non-fatal MI, non-fatal ischemic stroke or hospitalization for heart failure, unstable angina or coronary revascularization occurred in 12.8% (n=1,059) of patients receiving Onglyza and 12.4% (n=1,034) of patients receiving placebo (HR=1.02, 95% CI: 0.94, 1.11, p=0.66). More patients in the Onglyza arm were hospitalized for heart failure compared to the placebo arm (3.5% vs. 2.8%, HR=1.27, 95% CI: 1.07, 1.51, p=0.007). There was no significant difference in all-cause mortality between Onglyza and placebo (4.9% vs. 4.2%, HR=1.11, 95% CI: 0.96, 1.27, p=0.15). Furthermore, a significantly greater proportion of patients in the Onglyza arm reported ≥1 hypoglycemic event vs. placebo (15.3% vs. 13.4%, p<0.001), though there was no significant difference in the rate of hospitalization for hypoglycemia.

The trial enrolled patients with Type II diabetes who had either a history of established cardiovascular disease or multiple risk factors, with or without renal impairment, to receive once-daily 2.5 or 5 mg Onglyza or placebo with or without other anti-diabetic therapies. Data were published in the New England Journal of Medicine and presented at the European Society of Cardiology meeting in Amsterdam.

Onglyza is approved in 86 countries, including the U.S. and countries in the EU, as an adjunct to diet and exercise to improve glycemic control in adults with Type II diabetes. Bristol-Myers and AstraZeneca partnered in 2007 to develop and commercialize Onglyza, while Otsuka has rights in Japan (see BioCentury, Jan. 15, 2007). Kyowa Hakko Kirin Co. Ltd. (Tokyo:4151, Tokyo, Japan) has exclusive, Japanese rights to commercialize Onglyza under a June 2012 deal with Otsuka (see BioCentury, July 2, 2012).

**Resverlogix Corp.** (TSX:RVX), Calgary, Alberta

**Product**: RXV-208

**Business**: Cardiovascular

**Molecular target**: Bromodomain containing 4 (BRD4); Apolipoprotein A-1 (APOA1)

**Description**: Inhibitor of the BET family of bromodomain-containing proteins, including bromodomain containing 4 (BRD4)

**Indication**: Treat atherosclerosis in patients with acute coronary artery disease (CAD)

**Endpoint**: Reduction of 0.6% in atheroma volume from baseline to week 26 as measured by intravascular ultrasound (IVUS); change in total atheroma volume, percent change in APOA1 and HDL-C and safety

**Status**: Additional Phase Ib data

**Milestone**: NA

A subgroup analysis of 92 patients with median baseline HDL-C levels of <39 mg/dL who were taking either rosuvastatin or atorvastatin in the double-blind, placebo-controlled, international Phase Ib ASSURE trial in 281 evaluable high-risk CAD patients showed that twice-daily 100 mg
Clinical Results, from previous page

oral RVX-208 plus rosuvastatin led to a 1.43% reduction in atheroma volume from baseline to week 26 as measured by IVUS (p<0.002). RVX-208 plus atorvastatin led to a 0.19% increase from baseline to week 26 on the endpoint. Additionally, RVS-208 plus rosuvastatin led to a 12.3 mm\(^3\) reduction in total atheroma volume from baseline (p=0.0001) and a 4.3 mm\(^3\) reduction in atheroma volume in the 10 mm most diseased segment of the coronary arteries from baseline (p<0.0001). Compared to baseline, RVX-208 plus atorvastatin also led to an 18.2% improvement in HDL-C, a 16.4% improvement in APOA1 and a 74.7% improvement in large HDL-C particles (p<0.0001 for all). The trial was led by the Cleveland Clinic.

In June, Resverlogix reported top-line data from ASSURE showing that RVX-208 missed the primary endpoint of a 0.6% reduction in atheroma volume from baseline to week 26 as measured by IVUS. RVX-208 did meet the secondary endpoints of regression of total atheroma volume and increases in APOA1 and HDL-C (see BioCentury, July 1). RVX-208 is also in Phase II testing for pre-diabetes. Pfizer Inc. (NYSE: PFE, New York, N.Y.) markets Lipitor atorvastatin and AstraZeneca plc (LSE: AZN; NYSE: AZN, London, U.K.) markets Crestor atorvastatin and Astrazeneca's (LSE: AZN; NYSE: AZN, London, U.K.) markets Crestor rosuvastatin under a license from Shionogi & Co. Ltd. (Tokyo: 4507; Osaka: 4507, Osaka, Japan).

Rockwell Medical Technologies Inc. (NASDAQ:RMTI), Wixom, Mich.
Product: Soluble Ferric Pyrophosphate (SFP)
Business: Hematology
Molecular target: Transferrin
Description: Soluble form of iron in liquid bicarbonate
Indication: Treat iron deficiency anemia in chronic kidney disease (CKD) patients requiring hemodialysis
Endpoint: Mean change from baseline in hemoglobin; reticulocyte hemoglobin concentration, serum ferritin levels vs. placebo. Specifically, reticulocyte hemoglobin concentration declined 1.6% from baseline in the SFP arm vs. 2.6% in the placebo arm (p=0.017). Serum ferritin levels declined 11.6% from baseline in the SFP arm vs. 21.7% in the placebo arm (p<0.001). There were no differences in the frequency or severity of adverse events or serious adverse events between treatment groups. The trial enrolled patients with CKD on regular hemodialysis who were receiving stable doses of erythropoietin stimulating agents (ESAs) and who were iron replete. In July, Rockwell reported that SFP met the primary endpoint in the identical Phase III CRUISE-1 trial (see BioCentury, July 15). Rockwell plans to submit an NDA to FDA for SFP around 1Q14.

Milestone: Submit NDA (1Q14)

Top-line data from the double-blind, dose-ranging, crossover, New Zealand Phase IIb Study 0091 in 62 patients with moderate to severe COPD showed that all 6 doses of once-daily TD-4208 as a nebulized aqueous solution met the primary endpoint of improving trough FEV1 from baseline to day 7 vs. placebo. The trial evaluated 22, 44, 88, 175, 350 and 700 µg doses of TD-4208. Patients received placebo and 4 of the 6 doses of TD-4208 — each for 7 days. The 175 µg dose of TD-4208 led to a placebo-adjusted difference of 11.4 mL in trough FEV1 (p<0.001), with placebo-adjusted differences in trough FEV1 for all doses of TD-4208 ranging from 53-114 mL (p<0.01 for all).

Additionally, TD-4208 led to comparable bronchodilation over the first and second 12-hour periods on day 7 as measured by serial FEV1 measurements. TD-4208 also showed a low peak to trough ratio for TD-4208 consistent with a once-daily dosing regimen. All doses of TD-4208 were generally well tolerated with rates of adverse events comparable to placebo. The most common adverse events were headache, cough and dyspnea. There were no placebo-adjusted increases in heart rate or any ECG parameter at any dose of TD-4208 at any time point. In April, Theravance announced plans to split into 2 publicly traded companies to separate its partnered late-stage respiratory assets from its R&D (see BioCentury, April 29). Theravance said it is reviewing the data to determine next steps for TD-4208, which will be part of Theravance Biopharma after the split.

PRECLINICAL RESULTS

Tekmira Pharmaceuticals Corp. (TSX:TKM; NASDAQ:TKMR), Burnaby, B.C.
Product: Anti-MARV siRNA
Business: Infectious
Indication: Treat Marburg virus infection
In guinea pigs, Tekmira’s anti-MARV siRNAs provided 100% protection against Marburg virus strains Angola, C667 and Ravn. The product is an RNAi therapeutic against Marburg virus formulated with Tekmira’s lipid nanoparticle (LNP) siRNA delivery technology. Data were published in the Journal of Infectious Diseases. In 2010, Tekmira received an NIH grant to develop RNAi therapeutics to treat Ebola and Marburg hemorrhagic fever viral infections.

CLINICAL STATUS

Ariad Pharmaceuticals Inc. (NASDAQ:ARIA), Cambridge, Mass.
Product: Iclusig ponatinib (formerly AP24534)
Business: Cancer
Molecular target: BCR-ABL tyrosine kinase; FMS-like tyrosine kinase 3 (FLT3) (CD135)
Description: Pan-BCR-ABL tyrosine kinase inhibitor (TKI)
Indication: Treat chronic myelogenous leukemia (CML)
Endpoint: Major molecular response (MMR) rate at 12 months; MMR at 5 years, molecular response at 3 months, complete cytogenetic response at 12 months, progression-free survival (PFS) and overall survival (OS)
Status: Phase III ongoing
Milestone: Complete Phase III enrollment (year end 2013); Phase III interim data (3Q14)
Ariad said it has enrolled about 264 of a planned 500 newly diagnosed CML patients in the open-label, international Phase III EPIC trial comparing 45 mg oral Iclusig ponatinib daily vs. oral imatinib daily. Ariad plans to conduct a planned interim efficacy analysis of the primary endpoint of MMR at 12 months in 3Q14. The trial protocol specified that an interim analysis be conducted 12 months after half of the patients in the trial have been randomized. The company said that depending on the results, it may submit regulatory applications for Iclusig as front-line treatment of CML based on the interim...
Clinical Status, from previous page

data, which would be about 6 months earlier than submission with full data. Ariad expects data from EPIC to support accelerated approval for the indication in the U.S., as well as regulatory applications in the EU and Japan. In December, FDA granted accelerated approval to Iclusig for CML and Philadelphia-chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) that is resistant or intolerant to prior treatment with tyrosine kinase inhibitors (TKIs) (see BioCentury, Dec. 17, 2012). The European Commission approved Iclusig in July (see BioCentury, July 15). The product is under review in Canada and Australia and has Orphan Drug status to treat CML and Ph+ ALL in the U.S. and EU.

Ariad expects data from EPIC to support accelerated approval for the indication in the U.S., as well as regulatory applications in the EU and Japan. In December, FDA granted accelerated approval to Iclusig for CML and Philadelphia-chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) that is resistant or intolerant to prior treatment with tyrosine kinase inhibitors (TKIs) (see BioCentury, Dec. 17, 2012). The European Commission approved Iclusig in July (see BioCentury, July 15). The product is under review in Canada and Australia and has Orphan Drug status to treat CML and Ph+ ALL in the U.S. and EU.

**ArQule Inc.** (NASDAQ:ARQL), Woburn, Mass.

**Daichi Sankyo Co. Ltd.** (Tokyo:4568; Osaka:4568), Tokyo, Japan

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

**Product:** Tivantinib (ARQ 197)

**Business:** Cancer

**Molecular target:** c-Met receptor tyrosine kinase

**Description:** Small molecule inhibitor of c-Met receptor tyrosine kinase

**Indication:** Treat hepatocellular carcinoma (HCC)

**Endpoint:** Overall survival (OS); progression-free survival (PFS) and safety

**Status:** Phase III ongoing

**Milestone:** NA

ArQule disclosed in an SEC filing that a DMC recommended reducing the dose of tivantinib to 120 mg from 240 mg twice daily in the double-blind, placebo-controlled, international Phase III METIV-HCC trial due to a higher incidence of neutropenia than was seen with the compound in a Phase II trial in the indication. The DMC also recommended that ArQule institute “enhanced patient monitoring procedures,” including increased attention to neutropenia incidence and neutrophil counts, to confirm the safety of the lower dose. The DMC will review data after an undisclosed number of patients have received the 120 mg dose to determine the safety profile of the dose and whether to recommend any further action. ArQule said the companies were not commenting on whether the timeline for trial recruitment may be delayed as a result of the amendment.

ArQule and partner Daiichi have an SPA from FDA for the trial, which is designed to enroll previously treated patients with inoperable HCC that is positive for c-Met based on a diagnostic. ArQule is co-developing tivantinib with Daiichi on a worldwide basis outside of certain Asian countries, where ArQule licensed rights to Kyowa in 2007 (see BioCentury, April 30, 2007 & Nov. 17, 2008).

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

**Product:** Olaparib (AZD2281, KU-0059436)

**Business:** Cancer

**Molecular target:** Poly(ADP-ribose) polymerase (PARP)

**Description:** Poly(ADP-ribose) polymerase (PARP) inhibitor

**Indication:** Maintenance treatment of ovarian cancer in patients with breast cancer early onset (BRCA) mutations

**Endpoint:** Progression-free survival (PFS); overall survival (OS), time to deterioration of health-related quality of life, PFS in patients with deleterious BRCA variant, time to progression (TTP), time to second progression, pharmacokinetics and safety

**Status:** Phase III started

**Milestone:** NA

AstraZeneca began the double-blind, placebo-controlled, Phase III SOLO 2 (ENGOT-Ov21) trial to evaluate 300 mg oral olaparib twice daily in about 264 patients with BRCA-mutated, platinum-sensitive, relapsed ovarian cancer who are in complete or partial response following ≥2 lines of platinum-based chemotherapy. AstraZeneca is conducting the trial with the European Network of Gynecological Oncological Trial Groups. AstraZeneca will use the BRACAnalysis test from Myriad Genetics Inc. (NASDAQ:MYGN, Salt Lake City, Utah) as a companion diagnostic to select patients likely to respond to olaparib (see BioCentury, June 17).

In December 2011, AstraZeneca discontinued development of olaparib to treat serious ovarian cancer after an interim analysis of 265 patients in the Phase II Study 19 showed that a previously reported PFS benefit with olaparib as maintenance therapy was “unlikely to translate into an overall survival benefit.” AstraZeneca resumed development of the program after a retrospective analysis from a subgroup of patients with BRCA mutations from Study 19 showed that olaparib significantly improved median PFS vs. placebo in patients with germline BRCA mutations (11.2 vs. 4.1 months, p<0.001) (see BioCentury, May 27). As a result of starting the Phase III program, the pharma said a pre-tax impairment charge of $285 million incurred because of the discontinuation will be reversed and reflected in its 3Q13 earnings. The Phase III program also includes the Phase III SOLO 1 trial evaluating olaparib in BRCA-mutated ovarian cancer patients following first-line platinum-based chemotherapy.

**Indication:** Maintenance treatment of ovarian cancer in patients with breast cancer early onset (BRCA) mutations

**Endpoint:** Progression-free survival (PFS); overall survival (OS), time to deterioration of health-related quality of life, PFS in patients with deleterious BRCA variant, time to progression (TTP), time to second progression and safety

**Status:** Phase III started

**Milestone:** NA

AstraZeneca started the double-blind, placebo-controlled, Phase III SOLO 1 (GOG-3004) trial to evaluate 300 mg oral olaparib twice daily for up to 2 years in about 344 BRCA-mutated ovarian cancer patients who are in complete or partial response following first-line, platinum-based chemotherapy. AstraZeneca is conducting the trial with the Gynecologic Oncology Group. AstraZeneca will use the BRACAnalysis test from Myriad Genetics Inc. (NASDAQ:MYGN, Salt Lake City, Utah) as a companion diagnostic to select patients likely to respond to olaparib (see BioCentury, June 17).

In December 2011, AstraZeneca discontinued development of olaparib to treat serious ovarian cancer after an interim analysis of 265 patients in the Phase II Study 19 showed that a previously reported PFS benefit with olaparib as maintenance therapy was “unlikely to translate into an overall survival benefit.” AstraZeneca resumed development of the program after a retrospective analysis from a subgroup of patients with BRCA mutations from Study 19 showed that olaparib significantly improved median PFS vs. placebo in patients with germline BRCA mutations (11.2 vs. 4.1 months, p<0.001) (see BioCentury, May 27). As a result of starting the Phase III program, the pharma said a pre-tax impairment charge of $285 million incurred because of the discontinuation will be reversed and reflected in its 3Q13 earnings. The Phase III program also includes the Phase III SOLO 2 trial evaluating olaparib in BRCA-mutated, platinum-sensitive, relapsed ovarian cancer patients who are in complete or partial response following ≥2 lines of platinum-based chemotherapy.

**Besins Healthcare S.A., Bangkok, Thailand**

**Product:** BHR-100

**Business:** Inflammation

**Molecular target:** Progesterone receptor

**Description:** IV progesterone formulation

**Indication:** Treat severe traumatic brain injury (TBI)

**Endpoint:** Glasgow Outcome Scale (GOS) score at 6 months; mortality at 1 and 3 months after injury, GOS score at 3 months, GOS-Extended (GOS-E) score at 3 and 6 months, quality of life (QOL), intracranial pressure, cerebral perfusion pressure, therapeutic intensity level,
Transition Therapeutics Inc. (TSX:TTH; NASDAQ:TTHI), Toronto, Ontario

Elan Corp. plc (NYSE:ELN), Dublin, Ireland

BioDelivery Sciences International Inc. (NASDAQ:BDSI), Raleigh, N.C.

Chugai Pharmaceutical Co. Ltd. (Japan) (TSX:TTH; NASDAQ:TTHI), Toronto, Ontario

Chugai began an international, open-label, Phase I trial to evaluate once-daily oral Debio 1347 in patients with advanced solid tumors who have an alteration of the FGFR 1, 2 or 3 genes. An expansion phase of the trial will evaluate the recommended dose of Debio 1347 in a larger cohort of patients. Last December, Chugai granted Debiopharm exclusive, worldwide rights to develop and commercialize Debio 1347 (see BioCentury, Jan. 14).

Elan Corp. plc (NYSE:ELN), Dublin, Ireland

Elan began a double-blind, placebo-controlled, U.S. Phase IIa trial to evaluate once- and twice-daily oral 250 mg ELND005 for 4 weeks in about 24 patients with Down Syndrome without dementia. The compound, which has Fast Track designation to treat neuropsychiatric symptoms in Alzheimer’s disease (AD) patients, is also in Phase II testing to treat agitation and aggression in patients with AD and for maintenance treatment of bipolar I disorder. Elan and Transition partnered to develop ELND005 under an amended 2006 deal (see BioCentury, Oct. 2, 2006 & Jan. 3, 2011). Perrigo Co. (NASDAQ:PRGO; Tel Aviv:PRGO, Allegan, Mich.) is acquiring Elan (see BioCentury, Aug. 5).

Ohr Pharmaceutical Inc. (NASDAQ:OHRP), Salt Lake City, Utah

Product: Scyllo-inositol (AZD-103, ELND005)

Business: Neurology

Molecular target: Beta amyloid

Description: Small molecule that disaggregates beta amyloid fibrils

Indication: Treat cognitive dysfunction in Down Syndrome

Endpoint: Safety and changes in physical and neurological examinations; pharmacokinetics

Status: Phase IIa started

Milestone: NA

Clinical Status, from previous page

intracranial pathology and safety
Status: Completed Phase III enrollment
Milestone: Phase III data (05/2014)

BioDelivery and Endo said it will expand enrollment in the double-blind, placebo-controlled Phase III BUP-307 trial evaluating BEMA Buprenorphine in opioid-experienced patients with chronic lower back pain based on an interim analysis to maintain power of the study to allow for detection of statistical significance. The company, which declined to disclose the number of additional patients required, had previously planned to enroll 475 patients. Based on the interim analysis, the partners said no enrollment adjustments will be required for the double-blind, placebo-controlled Phase III BUP-308 trial evaluating BEMA Buprenorphine in opioid-naive patients with chronic lower back pain. The partners expect to report data from the BUP-308 trial early next year and now expect to complete the BUP-307 trial in mid-2014 — data from both trials were previously expected to be reported in 2H13 or early 2014. In 2012, BioDelivery granted Endo exclusive, worldwide rights to develop and commercialize BEMA Buprenorphine to treat chronic pain (see BioCentury, Jan. 9, 2012).

Debiopharm Group, Lausanne, Switzerland

Chugai Pharmaceutical Co. Ltd. (Tokyo:4519), Tokyo, Japan

Product: FF284, Debio 1347, CH5183284

Business: Cancer

Molecular target: Fibroblast growth factor receptor 1 (FGFR1) (CD331); Keratinocyte growth factor receptor (KGF) receptor (KGRF) (FGFR2) (CD332)

Description: Inhibitor of fibroblast growth factor receptor 1, 2 and 3

Indication: Treat advanced solid tumors

Endpoint: Dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and safety

Status: Phase I started

Milestone: NA

Debiopharm began an open-label, international Phase I trial to evaluate once-daily oral Debio 1347 in patients with advanced solid tumors who have an alteration of the FGFR 1, 2 or 3 genes. An expansion phase of the trial will evaluate the recommended dose of Debio 1347 in a larger cohort of patients. Last December, Chugai granted Debiopharm exclusive, worldwide rights to develop and commercialize Debio 1347 (see BioCentury, Jan. 14).

Imaxio S.A., Saint-Beauzire, France

Product: MVA85A-IMX313

Business: Infectious

Molecular target: NA

Description: Viral vector vaccine encoding antigen 85A fused to Imaxio’s IMX313 antigen re-engineering technology

Indication: Prevent tuberculosis (TB) infection

Endpoint: Safety; immune response

Status: Phase I started

Milestone: NA

Imaxio said researchers at the Jenner Institute at Oxford University began a single-blind, dose-escalation, U.K. Phase I trial to evaluate intradermal MVA85A-IMX313 vs. MVA85A alone in about 30 healthy Bacille Calmette-Guerin (BCG)-vaccinated healthy volunteers ages 18-55.

Neurocrine Biosciences Inc. (NASDAQ:NBIX), San Diego, Calif.

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

Product: Elagolix (NBI-56418, ABT-620)

Business: Genitourinary

Molecular target: GnrH/LHRH receptor

Description: Non-peptide small molecule gonadotropin-releasing hormone (GnRH) antagonist

Indication: Treat endometriosis

Endpoint: Endometriosis-associated pain, bone mineral density (BMD), endometrial thickness and proportion of patients with ovarian cyst; safety and pharmacokinetics

Status: Phase III started

Milestone: Phase III data (3Q14); submit NDA (2016)

Neurocrine said AbbVie began the double-blind, placebo-controlled, international Phase III M12-671 trial to evaluate 2 doses of elagolix for 6 months in 788 women ages 18-49 years with moderate to severe endometriosis-associated pain. Neurocrine said top-line data from the similar Phase III M12-665 trial, which began last year, are expected in 3Q14 (see BioCentury, July 23, 2012). Neurocrine granted Abbott Laboratories (NYSE:ABT, Abbott Park, Ill.) exclusive, worldwide rights to develop and commercialize elagolix in 2010 (see BioCentury, June 21, 2010). Abbott spun out its pharmaceuticals business into AbbVie in January.

Ohr Pharmaceutical Inc. (NASDAQ:OHRP), Salt Lake City, Utah

Product: Squalamine eye drops (OHR-002)

Business: Ophthalmic

Molecular target: Calmodulin

See next page
Clinical Status, from previous page

Description: Topical eye drop formulation of the synthetic small molecule anti-angiogenic aminosterol
Indication: Treat central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO)
Endpoint: Visual acuity parameters; need for rescue treatments, retinal thickness, vascular leakage and change in area of non-perfusion
Status: Trial started
Milestone: NA data (2014)

Ohr said the Cumberland Valley Retina Consultants began the Study OHR-004 trial to evaluate squalamine eye drops in about 20 treatment-naïve patients. Patients will receive squalamine eye drops for 2 weeks followed by 2 successive injections of Lucentis ranibizumab 4 weeks apart while continuing to receive squalamine eye drops. At week 10, patients will be randomized to continue treatment with squalamine eye drops or discontinue treatment for the remainder of the 38-week treatment period, with rescue injections of Lucentis administered as needed. Genentech Inc., a unit of Roche (SIX:ROG; OTCQX:RHHBY, Basel, Switzerland), markets Lucentis in the U.S., while Novartis AG (NYSE:NVS; SIX:NOVN, Basel, Switzerland) markets it elsewhere.

Orexo AB ( SSE: ORX), Uppsala, Sweden
Kyowa Hakko Kirin Co. Ltd. (Tokyo:4151), Tokyo, Japan
Product: Abstral fentanyl (Rapinyl) (EN 3267, KW-2246)
Business: Neurology
Molecular target: Opioid receptor (OPR)
Description: Sublingual mucoadhesive fentanyl
Indication: Treat breakthrough cancer pain
Endpoint: NA
Status: Postmarketing study started
Milestone: NA


Proteus S.A., Santiago, Chile
Product: Neosaxitoxin
Business: Neurology
Molecular target: NA
Description: Site 1 sodium channel blocker
Indication: Provide long-acting local anesthesia
Endpoint: Safety; pharmacokinetics, cutaneous sensory blockade and local skin reactions
Status: Phase I started
Milestone: NA

Proteus said Boston Children’s Hospital began a double-blind, placebo-controlled, dose-escalation, U.S. Phase I trial to evaluate 5, 15, 30, 45, 60 and 70 µg subcutaneous neosaxitoxin with and without 0.2% bupivacaine in about 77 healthy volunteers.

SanBio Inc., Mountain View, Calif.
Product: SB623
Business: Neurology
Molecular target: NA
Description: Allogenic cells derived from genetically engineered bone marrow stromal cells obtained from healthy adult donors
OFFERINGS & SECURITIES TRANSACTIONS

Week ended 9/6/13. Shares after offering refers to shares outstanding. Proceeds are gross, net net. Shares offered don’t include overallotments. Currency rates used in the week: A$=$0.8964; CS=$0.95003; DKK=$0.17708; £=$1.3209; ¥=$1.5554; NOK=$0.16358

Completed Offerings

Acacia Pharma Ltd., Cambridge, U.K.
Business: Gastrointestinal, Endocrine/Metabolic, Other
Date completed: 9/3/13
Type: Venture financing
Raised: £15 million ($23.3 million)
Investors: Fidelity Biosciences; Novo; Gilde Healthcare Partners; LundbeckFond Ventures

Affinium Pharmaceuticals Ltd., Austin, Texas
Business: Infectious, Computational chemistry/biology
Date completed: 9/4/13
Type: Venture financing
Raised: Not disclosed
Investors: Existing investors
Note: Affinium raised an undisclosed amount in an extension of an undisclosed venture round.

Algeta ASA (OSE:ALGETA), Oslo, Norway
Business: Cancer
Date completed: 9/4/13
Type: Convertible bond financing
Raised: $120 million
Underwriters: ABG Sundal Collier; Goldman Sachs; DnB NOR Markets
Note: The convertible senior unsecured bonds bear a 3.4% coupon, initially convert at $52.50 and mature in 2018.

Arsanis Inc., Vienna, Austria
Business: Antibodies
Date completed: 9/3/13
Type: Venture financing
Raised: $20 million
Investors: NeoMed; OrbiMed Advisors; Polaris Venture Partners; SV Life Sciences

BioPorto Diagnostics A/S (CSE:BIOPOR), Gentofte, Denmark
Business: Diagnostic, Antibodies

Catalyst Pharmaceutical Partners Inc. (NASDAQ:CPRX), Coral Gables, Fla.
Business: Neurology
Date completed: 9/5/13
Type: Direct public offering
Raised: $15.1 million
Shares: 8.8 million
Price: $1.72
Shares after offering: 52.9 million
Placement agent: Roth Capital Partners

ContraFect Corp., Yonkers, N.Y.
Business: Infectious, Antibodies
Date completed: 9/4/13
Type: Venture financing
Raised: $11.8 million
Placement agent: Maxim Group
Note: The offering was comprised of convertible notes.

Critical Outcome Technologies Inc. (TSX-V:COT), London, Ontario
Business: Cancer, Autoimmune, Infectious
Date completed: 8/28/13
Type: Private placement of units
Raised: C$596,995 (US$567,145)
Units: 5 million
Price: C$0.12 (unit)
Shares after offering: 91.6 million
Note: Critical Outcome raised $30 million in the second tranche of a unit offering, bringing the total raised to $1.1 million ($1 million). Each unit comprises a share and an 18-month warrant to purchase a share at C$0.26. The company raised C$500,010 ($475,015) in August.
Date completed: 8/30/13
Type: Private placement of units
Raised: C$128,004 (US$121,604)
Units: 1.1 million
Price: C$0.12 (unit)
Shares after offering: 92.7 million
Note: Critical Outcome raised C$128,000 ($121,604) in the third tranche of a unit offering, bringing the total raised to C$1.2 million ($1.2 million). Each unit comprises a share and an 18-month warrant to purchase a share at C$0.26.

Cubist Pharmaceuticals Inc. (NASDAQ:CBST), Lexington, Mass.
Business: Infectious
Date completed: 9/5/13
Type: Private placement of convertible notes
Raised: $700 million
Note: The unsecured notes offering comprises $300 million in 1.875% notes due 2020. Both sets of notes initially convert at $82.43. On Sept. 3, Cubist proposed to raise $600 million in the offering.

Eagle Genomics Ltd., Cambridge, U.K.
Business: Bioinformatics
Date completed: 9/2/13
Type: Venture financing
Raised: £590,000 ($917,686)
Investors: Midven; Cambridge Angels; London Business Angels; Cambridge Capital Group; and other investors
Note: Eagle Genomics raised £590,000 ($917,686) in the first close of a planned £1 million ($1.6 million) round.

Intra-Cellular Therapies Inc., New York, N.Y.
Business: Neurology
Date completed: 9/3/13
Type: Venture financing
Raised: $60 million
Investors: Deerfield Management; Broadfin Capital; existing investors
Placement agent: Leerink
Note: Intra-Cellular raised about $60 million and then reverse-merged with an undisclosed publicly listed shell company. Intra-Cellular raised about $44.7 million through the sale of about 18.9 million shares in a private placement and about $15.3 million through the conversion of bridge notes. Intra-Cellular said it plans to list on an OTC market but declined to disclose details. Intra-Cellular’s ITI-007, a dual serotonin (5-HT2A) receptor antagonist and dopamine receptor phosphoprotein modulator (DPPM), is in Phase II testing to treat schizophrenia.

iPierian Inc., South San Francisco, Calif.
Business: Neurology, Gene/Cell therapy
Date completed: 9/4/13
Type: Venture financing
Raised: Not disclosed
Investors: SR One; Kleiner Perkins Caufield & Byers; MPM Capital; Biogen Idec New Ventures; Highland Capital Partners; Google Ventures; FinTech Global Capital; Mitsubishi UFJ Capital Co.; ATEL Ventures
Note: iPierian raised an undisclosed amount of a $30 million venture round. An undisclosed portion of the financing will be allocated to spin out True North Therapeutics Inc. (South San Francisco, Calif.).

Leukocare AG, Martinsried, Germany
Business: Supply/Service
Date completed: 9/3/13
Type: Venture financing
Raised: €2.4 million ($3.2 million)
Investors: Existing investors; new investors
Note: The company also converted an €1 million ($1.3 million) corporate bond.

Mind-NRG, Geneva, Switzerland
Business: Neurology
Date completed: 9/4/13
Type: Venture financing
Raised: €6 million ($7.9 million)
Investors: LRM N.V.; Index Ventures

Otonomy Inc., San Diego, Calif.
Business: Other, Drug delivery, Infectious
Date completed: 9/4/13
Type: Venture financing
Raised: $45.9 million
See next page
Completed Offerings, from previous page

Investors: Orbis Med Advisors; Aperture Venture Partners; Osage University Partners; Avalon Ventures; Domain Associates; Novo Ventures; RiverVest Venture Partners; TPG Biotech

Triton Algae Innovations Ltd., San Diego, Calif.
Business: Gastrointestinal, Cancer
Date completed: 9/4/13
Type: Venture financing
Raised: $5 million
Investor: Heliae Technology Holdings

True North Therapeutics Inc., South San Francisco, Calif.
Business: Hematology, Renal, Neurology
Date completed: 9/4/13
Type: Venture financing
Raised: Not disclosed
Investors: SR One; Kleiner Perkins Caufield & Byers; MPM Capital; Biogen Idec New Ventures
Note: The company, which iPierian Inc. (South San Francisco, Calif.) spun out to develop TINT009, raised an undisclosed amount in a series A round. TINT009 is a mAb inhibitor of an undisclosed target in the complement pathway in preclinical development to treat complement-mediated rare diseases in hematologic, renal and neurologic areas.

Proposed Offerings

Amarantus Bioscience Holdings Inc. (OTCQB:AMBS), Sunnyvale, Calif.
Business: Neurology, Cardiovascular
Date announced: 9/4/13
Type: Private placement of convertible debentures and warrants To be raised: $1.4 million
Price prior: $0.08
Shares outstanding prior: 461 million
Investors: Institutional investors
Note: The debenture bears 8% interest and converts at $0.04. The investors will also receive three-year warrants to purchase shares at $0.06.

Clavis Pharma ASA (OSE: CLAVIS), Oslo, Norway
Business: Drug delivery, Cancer, Infectious
Date announced: 9/4/13
Type: Rights offering of units To be raised: Up to NOK54 million ($8.8 million)
Price prior: NOK1.82
Advisor: Carnegie Shares outstanding prior: 33.8 million
Investors: Existing investors
Note: Shareholders will receive one subscription right for each share held.

Cyprotex plc (LSE:CRX), Macclesfield, U.K.
Business: ADMET
Date announced: 8/7/13
Type: Private placement of notes
To be raised: Up to £7 million ($10.9 million)
Shares outstanding prior: 224.3 million
Investor: Hardwood Capital
Note: Hardwood Capital agreed to subscribe for a £3 million ($4.7 million) loan. Additionally, Hardwood agreed to subscribe for any convertible loan notes which are not subscribed for by shareholders under a £4 million ($6.2 million) open offer. The convertible loans will convert at 6p per share.

MacroGenics Inc., Rockville, Md.
Business: Cancer, Autoimmune, Infectious
Date announced: 9/5/13
Type: IPO
To be raised: Up to $60 million
Shares: TBD
Price: TBD
Underwriters: BoA Merrill Lynch; Leerink; Stifel Nicolaus Weisel; Wedbush

Mimetica Pty. Ltd., Milton, Australia
Business: Dermatology
Date announced: 8/7/13
Type: Private placement
To be raised: Up to A$6.5M ($5.8 million)
Shares: 26 million
Price: A$0.25
Placement agent: Phillip Capital
Investors: Queensland Investment Corp.; existing investors
Note: The shares outstanding figure reflects the acquisition of all Mimetica shares by Telesso Technologies Ltd. and a 6.7-for-1 reverse stock split of existing Telesso shares. The newco, which will be named Mimetica Ltd., expects to relist on ASX on Oct. 15.

Fate Therapeutics Inc., San Diego, Calif.
Business: Gene/Cell therapy, Cancer, Musculoskeletal
Date announced: 9/3/13
Type: IPO
To be raised: Up to $73.6 million
Shares: 4 million
Price: $14-$16
Underwriters: Cowen; BMO Capital Markets; Wedbush
Over allotment: 600,000
Note: Fate Therapeutics amended its IPO and now plans to sell 4 million shares at $14-$16. The company filed to raise up to $69 million in August.

Five Prime Therapeutics Inc., South San Francisco, Calif.
Business: Cancer, Autoimmune, Inflammation
Date announced: 7/26/13
Type: IPO
To be raised: Up to $60 million
Shares: 4 million
Price: $12-$14
Underwriters: Jefferies; BMO Capital Markets; Wells Fargo; Guggenheim Securities
Over allotment: 600,000
Note: Five Prime amended its IPO and now plans to sell 4 million shares at $12-$14. The company filed to raise up to $60 million in July.

Amended Offerings

AcCELERON PHARMA INC., Cambridge, Mass.
Business: Musculoskeletal, Hematology, Cancer
Date announced: 8/7/13
Type: IPO
To be raised: Up to $80.2 million
Shares: 4.7 million
Price: $13-$15
Underwriters: Citigroup; Leerink; Piper Jaffray; JMP Securities
Over allotment: 697,500
Note: Acceleron amended its IPO and now plans to sell 4.7 million shares at $13-$15. In August, the company filed to raise up to $74.8 million. Partner Celgene Corp. (NASDAQ:CELG, Summit, N.J.) has agreed to purchase $10 million in shares in a concurrent private placement.

Bind Therapeutics Inc., Cambridge, Mass.
Business: Cancer, Drug delivery
Date announced: 9/5/13
Type: IPO
To be raised: Up to $86.5 million
Shares: 4.7 million
Price: $14-$16
Underwriters: Credit Suisse; Cowen; Stifel, Nicolaus & Co.; JMP Securities
Over allotment: 705,000
Note: Bind amended its IPO and now plans to sell 4.7 million shares at $14-$16. The company filed to raise up to $80.5 million in August.

Fate Therapeutics Inc., San Diego, Calif.
Business: Gene/Cell therapy, Cancer, Musculoskeletal
Date announced: 9/3/13
Type: IPO
To be raised: Up to $73.6 million
Shares: 4 million
Price: $14-$16
Underwriters: Cowen; BMO Capital Markets; Wedbush
Over allotment: 600,000
Note: Fate Therapeutics amended its IPO and now plans to sell 4 million shares at $14-$16. The company filed to raise up to $69 million in August.

Other Financial News

ALK-ABELO A/S (CSE:ALK-B), Horsholm, Denmark
Business: Inflammation
Date announced: 9/5/13
ALK-ABELO established a level I ADR program on the OTC market. Five ADRs represent one ordinary share and will trade under the symbol “AKABY.” Deutsche Bank is the depository bank.

Alpine BioVentures, Seattle, Wash.
Business: Finance
Date announced: 9/3/13
Mitchell Gold, former president and CEO of immunother-
apy cancer company Dendreon Corp. (NASDAQ:DNDN, Seattle, Wash.), and biotech analyst David Miller launched biotech hedge fund Alpine BioVentures. Miller said Alpine will start as a “modestly sized fund” in the “multiple millions,” but the target size of the fund is not disclosed. The fund will primarily focus on development-stage public biotechs but may also invest in private companies primarily in cancer and Orphan diseases. Gold left Dendreon last year and is chairman of Alpine Biosciences Inc. (Seattle, Wash.), which he founded last year to develop next-generation cancer immunotherapies. Miller was CEO of biotech research firm Biotech Stock Research LLC, which he co-founded in 1999.

Business: Cancer, Infectious
Date announced: 9/3/13
Cel-Sci said NYSE MKT accepted the company’s plan to regain compliance with requirements for continued listing. The company has until Sept. 30 to regain compliance.

Corgenix Medical Corp. (OTCBB:CONX), Broomfield, Colo.
Business: Diagnostic
Date announced: 9/4/13
Corgenix entered into a one-year, $1.5 million secured revolving credit facility with Bank of the West. The facility bears interest at the one-month LIBOR rate plus 4%. Corgenix said the facility replaces an expiring $1.5 million credit facility with LSQ Funding Group.

Heat Biologics Inc. (NASDAQ:HTBX), Chapel Hill, N.C.
Business: Cancer, Inflammation
Date announced: 9/5/13
Heat Biologics raised $1 million through the sale of 100,000 shares at $10 to cover the overallotment from its July 23 IPO, bringing the total raised to $27 million. The company, which closed Friday at $9.75, has 6.3 million shares outstanding.

KaloBios Pharmaceuticals Inc. (NASDAQ:KBIO), South San Francisco, Calif.
Business: Antibodies, Infectious, Inflammation
Date announced: 9/3/13
KaloBios filed a shelf registration covering the sale of up to $100 million of its securities. The company, which closed Friday at $9.75, has 6.3 million shares outstanding.

NewLink Genetics Corp. (NASDAQ:NLNK), Ames, Iowa
Business: Cancer
Date announced: 9/5/13
NewLink established an at-the-market program to sell up to $60 million of its common stock. Cantor Fitzgerald & Co. is the sales agent.

Opexa Therapeutics Inc. (NASDAQ:OPXA), The Woodlands, Texas
Business: Autoimmune, Gene/Cell therapy
Date announced: 9/4/13
Opexa raised $757,000 through the sale of 650,000 shares at $1.15 to cover the overallotment from its Aug. 8 follow-on, bringing the total raised to $19 million. The company, which closed Friday at $1.53, has 20.8 million shares outstanding.

OvaScience Inc. (NASDAQ:OVAS), Cambridge, Mass.
Business: Reproductive
Date announced: 8/30/13
OvaScience filed a shelf registration covering the sale of up to $100 million of its securities. The company, which closed at $13.16 on Friday, has 16.9 million shares outstanding.

PDL BioPharma Inc. (NASDAQ: PDLI), Incline Village, Nev.
Business: Antibodies
Date announced: 9/4/13
PDL BioPharma amended the conversion rates for its outstanding convertible senior notes in connection with its regular dividend to be paid on Sept. 12 to stockholders of record on Sept. 5. The 2.875% convertible senior notes due Feb. 15, 2015, convert into 179.8 shares per $1,000 principal amount, up from 174.4 shares. The 3.75% notes, due May 1, 2015, convert into 157.4 shares per $1,000 principal amount, up from 154.4 shares.

Sanderling Ventures, San Mateo, Calif.
Business: Finance
Date announced: 9/5/13
Sanderling Ventures secured $30 million from BDC Venture Capital and Fonds de solidarite FTQ for a Canadian fund that Sanderling said will operate in parallel to its Sanderling VII fund, which is targeting $250 million. BDC will contribute $20 million and Fonds de solidarite will contribute $10 million. In connection with the commitment, Sanderling said it will establish a permanent center in Montreal to help develop early stage life science projects. Sanderling could not be reached for details, including how much the firm is targeting for its Canadian fund and when it expects to close Sanderling VII. Sanderling emphasizes early stage financing and active management of its portfolio companies.

UCB Group (Euronext:UCB), Brussels, Belgium
Business: Neurology, Autoimmune, Inflammation
Date announced: 9/3/13
UCB said it will exchange up to €250,000 ($330,225) of its €750,000 ($990,675) outstanding in 5.75% notes due Nov. 27, 2014 for new 5.125% notes due Oct. 2, 2023. BNP Paribas Fortis, ING Bank and KBC Bank are deal managers and joint bookrunners while ING Bank is also global coordinator.