Blockbusted at ODAC

BioCentury This Week

Cover Story
Blockbusted — Last week’s ODAC meeting on the safety of ESAs from Amgen and J&J marked the beginning of a long process that will narrow the approved indications in the blockbuster chemotherapy-induced anemia market, with an advisory committee now set up to review renal indications in the fall.

A Roll of the Dice — ODAC’s thumbs down for IDM’s Junovan and the approvable letter for Dendreon’s Provenge may harden beliefs that FDA imposes unreasonable hurdles on innovative cancer treatments, but Junovan arguably was a long shot.

Strategy
Bigger Platform for Product Deals — Peptech beefed up its antibody platform by acquiring EvoGenix, which it reckons should allow it to pursue organic growth and make it a more attractive suitor.

Product Development
Silencing a Silent Killer — Isis and Bristol-Myers are betting on a gene silencing approach to target PCSK9, which has been linked to hypercholesterolemia, because the specific cellular substrate of the enzyme is unknown.

Technology Briefing
Sodden Dance — Researchers have identified a toxic factor related to mutant glial cells that may play a direct role in the degeneration of neurons associated with ALS.

Terpene Assembly Line — UC Berkeley researchers have engineered E. coli to produce functional plant-derived terpenoids, which could drastically reduce the cost of pharmaceutical production of these compounds.

Emerging Company Profile
Finding a Peg That Fits — Complex Biosystems says its TransPEG transient pegylation technology can be applied to peptides and small proteins while preserving the pharmacology of the original protein.

Politics & Policy
Amending FDARA — The U.S. Senate has passed its version of the PDUFA reauthorization, but the House has yet to begin piecing together its package.

Ebb & Flow
Striking While the Iron is Hot — Capitalizing on the Provenge window. Prostate plays. Portola, Targanta build runway. Biodel’s uptick. Addex on deck. VCs: Nextech; Emergent; Sofinnova Ventures; Vivo. Banks: Cowen; Seymour Pierce. Also: Inspire; Ista; NicOx; Karo Bio; Speedel, et al.

Queen Moves in Chess Game — PDL Biopharma co-founder Cary Queen has aligned himself with hedge fund Third Point’s campaign to oust CEO Mark McCade.

Playing the China Market — More Chinese drug companies are likely to try U.S. IPOs to tap into investor interest in China’s enormous healthcare market and to use U.S. shares as currency to play consolidator at home.

Online this week
Stock charts & tables
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By Steve Usdin
Washington Editor
Last week’s Oncologic Drugs Advisory Committee meeting marked the beginning of a process that will narrow the approved indications for erythropoiesis-stimulating agents to treat anemia due to cancer chemotherapy. Label changes are likely to be made incrementally as the agency receives and evaluates data, in some cases based on recommendations from future ODAC meetings.

The first bite could take a large slice off the U.S. market for Aranesp darbepoetin alfa from Amgen Inc. and Procrit epoetin alfa from Johnson & Johnson (NJ.) to treat chemotherapy-induced anemia (CIA).

Meanwhile, ODAC also put the final nail in the coffin for the off-label use of ESAs in specific types of cancer, includes the possibility that FDA will indicate that ESAs should not be administered to breast cancer or head and neck cancer patients. That move will probably come later, and it is difficult to assess how deep it will be.

Queen (AMGN, Thousand Oaks, Calif.) has a lot of skin in this game. In 2006, Aranesp posted U.S. oncology sales of $2.1 billion, including $1.4 billion for CIA, $500 million for AoC, and $200 million for myelodysplastic syndromes (MDS). Outside the U.S., AMGN sold $500 million of Aranesp for cancer, all for CIA.

BioEquity Europe Update
Ready to congregate in Scotland next week.
Please see announcement following A28.
Regulation, from previous page

except $50-$70 million from AoC and a smaller amount for MDS.

JNJ does not break out the use of its ESAs by indication, but overall U.S. sales of Procrit in 2006 were $527 million and worldwide sales of Procrit/Eprex were $786 million.

ODAC’s unambiguous 16-1 recommendation to restrict use of ESAs in CIA indications was based on emerging safety signals, as well as concerns that advertising and financial incentives have stimulated medically inappropriate use of the products (see “ODAC, Pazdur Agree on DTC,” A9).

FDA’s refusal to allow sponsors to put any quality of life claims on ESA labels for CIA strongly influenced the committee’s assessment of the benefits the class provides in this indication.

ODAC’s recommendations also were based on the committee’s and FDA’s views that AMGN (Thousand Oaks, Calif.) and JNJ have not been sufficiently diligent in conducting safety studies and in ensuring the companies have access to studies conducted by third parties.

Even though ESAs have been approved for CIA since 1993, the committee concluded that pressing safety issues must be studied, that data suggesting that the class might cause tumor proliferation may warrant additional label restrictions, and that FDA should take steps to prevent use of Aranesp or Procrit in CIA patients who are not at risk of requiring a red blood cell transfusion.

All told, ODAC members cast six votes, disagreeing only once with the premise of the question posed by the agency. While the committee members endorsed strategies that would limit use of ESAs, they rejected the idea that the ceiling hemoglobin level already on the label be lowered (see “ODAC Votes”).

Unresolved

Safety concerns about the administration of ESAs to cancer patients are not new, although virtually all of the negative safety data come from trials that were conducted off-label, either to boost hemoglobin above the 12 g/dL recommended on the label to test the theory that this could improve the effectiveness of chemotherapy or radiation, or in AoC.

FDA convened ODAC in May 2004 to discuss negative safety signals from two European trials of ESAs. The Breast Cancer Erythropoietin Trial (BEST, EPO-INT-76) was a potentiation trial designed to study overall survival in breast cancer patients who received JNJ’s Eprex or placebo. It was terminated early, in April 2002, after an interim analysis showed lower one-year survival in the Eprex arm compared with placebo (70% vs. 76%, p=0.0117).

In another potentiation study, head and neck cancer patients in the ENHANCE trial who received NeoRecormon epoetin beta from Roche (SWX:ROG, Basel, Switzerland) from March 1997 to April 2001 had worse loco-regional control of head and neck cancer and lower overall survival than those who received placebo.

At the 2004 meeting, ODAC concluded that because the BEST and ENHANCE studies were focused on potentiation, the results should not be extrapolated to the overall CIA indication (see BioCentury, May 10, 2004).

AMGN and JNJ also noted at least eight trials were underway that would yield more relevant safety data. ODAC and FDA came away from the meeting expecting that the ongoing studies would resolve many of the lingering safety concerns about treating cancer patients with ESAs.

As last week’s meeting demonstrated, this has not happened.

In December 2006, a study of Aranesp to treat AoC in head and neck cancer patients was terminated early because a planned interim analysis showed no evidence of benefit from Aranesp. But it also showed a non-significant increase in death in the Aranesp arm, which reignited concerns about the safety of ESAs.

AMGN’s failure to publicly disclose the early termination of Study SE 2002-9001 also caused investors to question its transparency and prompted an informal SEC inquiry.

AMGN was relieved to announce the results of another trial, Study 145, in April this year. Although it failed to meet its endpoint, a survival advantage for Aranesp in advanced small cell lung cancer patients, the product was not associated with decreased survival (see BioCentury, April 23).

But at last week’s meeting, FDA argued it would be inappropriate to draw much comfort from Study 145. “Failure to show

See next page
superior survival with ESAs does not exclude the possibility of decreased survival," said medical reviewer Vinni Juneja.

Several members of the committee said they were frustrated by the lack of progress in clarifying questions that were raised three years ago. Indeed, a good part of last week’s discussion echoed complaints at the 2004 review.

Most of the safety data generated since the 2004 ODAC meeting come from trials conducted in off-label indications: AoC, potentiation of radiation and chemotherapy, and especially, targeting hemoglobin levels in CIA above the currently recommended 12 g/dL ceiling.

Indeed, AMGN and JNJ last week said they could submit only summary data for several of the studies because independent investigators are conducting them or they have not been completed.

Richard Pazdur, director of FDA’s Office of Oncology Drug Products, attacked AMGN for failing to obtain primary data from studies conducted by academic investigators. The fact that AMGN told ODAC in 2004 that critical safety data would be provided by some studies it was not sponsoring obligated the company to make sure it got the full data, Pazdur said, and its failure to do so represents a breach of that obligation.

“There was, especially after the 2004 meeting, considerable controversy over the safety of the drug,” he noted. “The sponsor had an obligation to work with the investigators prospectively after the 2004 meeting to provide us with all of the data.”

FDA also criticized JNJ for its conduct of an ongoing study in breast cancer patients, EPO-ANE-3010, that was designed to meet ODAC’s 2004 recommendations.

Study enrollment began in March 2006, but only 108 patients had been accrued as of March 2007. Because of slow accrual, the company has cut the study size to 1,000 from the original 2,000. Using non-inferiority benchmarks, if 1,000 patients are accrued, the trial will have a 90% power to exclude the possibility that progression-free survival in the treatment could be as much as 25% lower than the placebo group, while the 2,000-patient trial would have had an 80% power to exclude a 15% reduction in PFS in treated patients versus the placebo group.

ODAC did hear last week that in at least six studies, an ESA was associated with either decreased survival compared to placebo or cancer progression (see BioCentury, March 12).

With a single exception, all of the trials with negative survival or tumor progression outcomes were intended to achieve and maintain hemoglobin levels at or above 12 g/dL. The exception, Study 2001-0103, was for an off-label indication, patients with AoC who were not receiving chemotherapy or myelosuppressive radiotherapy.

At the meeting, AMGN and JNJ argued that because the studies sought to drive hemoglobin levels above 12 g/dL, the increase in deaths could not be directly extrapolated to standard medical practice.

ODAC members were not convinced, however, that the increased risk of death is limited to uses of ESAs that are now considered inappropriate. Their consensus was that while it is difficult or impossible to extrapolate from off-label trials to the approved CIA indication, the weight of the evidence sends a cautionary signal.

Several panel members said drug sponsors have an obligation to demonstrate the safety of their products and encouraged FDA to act on emerging or suboptimal negative safety data until and unless they are refuted by more robust data.

“The concern is, are these safety signals, albeit at doses that are not labeled, messages that need to be incorporated in the current label to maximize safety until we can conduct appropriate studies at appropriate doses?” said Gail Eckhardt, director of the division of oncology for the GI Malignancies Program at the University of Colorado Health Sciences Center. Eckhardt, a permanent ODAC member, chaired the meeting.

Chorus for change

ODAC’s 16-1 vote to recommend additional restrictions on ESA labels was motivated by concerns that physicians need more specific instructions on when the drugs should be used, and importantly, when they should not.

The vote represented a recommendation to place a “McDonald’s cup of coffee warning label: It is hot,” said Bruce Redman, associate professor of medicine at the University of Michigan Comprehensive Cancer Center. He served as a temporary voting member of ODAC.

ODAC was certain that ESAs are being over-used, and told FDA to place new language on labels to limit exposure of patients who are not anemic.

The warning on ESA labels that “hemoglobin concentration should not exceed 12 g/dL” might be too vague, suggested Patricia Keegan, director of FDA’s Division of Biologic Oncology Products. “We are aware that one interpretation of the labeling is that as soon as hemoglobin is less than 12, there are community physicians who believe you are eligible to begin ESAs.”

Keegan asked the committee: “Is that an appropriate practice?”

The committee answered almost as unequivocally, voting 15-2 to recommend that FDA define a maximum hemoglobin level at which ESA therapy should be initiated in asymptomatic patients. It left it up to FDA, acting on its own or on the basis of a future ODAC meeting, to set the threshold.

In an April 15 letter to FDA, the American Society of Hematology recommended that “ESAs be started in appropriate clinical settings at a hemoglobin level at or below 10 g/dL.”

National Comprehensive Cancer Network practice guidelines note that the 10 g/dL level is intended to prevent red blood cell transfusions.

“If an improvement in patient function is the goal,” NCCN recommends “11 g/dL as the level to consider intervention based on the eligibility criteria of the majority of the large community-based studies, the lag time for erythropoietin to improve hemoglobin, and the desire to maintain the hemoglobin in the 11 to 12 g/dL range for the longest duration during therapy.”

Establishing an initiation level of 11 or 10 g/dL of hemoglobin could have an impact on the ESA market, although the extent is not clear.

AMGN’s review of patient records indicates that “it is
extraordinarily rare for people to start [an ESA] at a hemoglobin above 12,” Roy Baynes, VP of global development, oncology supportive care, told the panel.

According to AMGN’s chart review, Baynes said 41% of oncology patients are started on an ESA when their hemoglobin is under 8, and 53% when it is between 8 and 10 g/dL.

The company previously has reported that 95% of ESA prescriptions for CIA in 2006 were for patients with hemoglobin levels below 12 g/dL and 72% were for patients with levels below 11 g/dL.

These numbers do not, however, translate directly to market size.

For example, setting an initiation threshold of 11 g/dL would not cut overall usage by 28% (the percent of patients who are started on treatment when their hemoglobin is at 11 or more). Rather, it would create a short-term decrease in ESA usage that would be at least partially reversed as some patients fall below the initiation threshold.

A JNJ-supported trial of small cell lung cancer (SCLC) patients who were randomized to Procrit or placebo in conjunction with chemotherapy sheds some light on the phenomenon.

Patients in the placebo arm of the N93-004 trial had a baseline hemoglobin of 13 g/dL. The mean hemoglobin level for the placebo patients fell below 11 g/dL at week five and decreased to 9.9 g/dL at week 14. By week 22, the mean hemoglobin level for the placebo patients had increased to 10.3 g/dL.

The degree of anemia — and therefore the number of patients who hit specific ESA initiation thresholds — also probably varies by treatment regimen.

In the BEST trial of women with metastatic breast cancer receiving first-line chemotherapy, patients in the placebo arm maintained the target 12-14 g/dL hemoglobin level for 45% of the 52 study weeks. Mean hemoglobin levels did not go below 11 g/dL in either arm.

**Lower ceiling**

While ODAC recommended that FDA set a target hemoglobin level for initiating ESAs, the committee brushed aside the agency’s suggestion that it might lower the ceiling on ESA labels from 12 g/dL.

The ESA sponsors presented “quality of life data that would support that 12 is better than 11, and 11 is better than 10,” Eckhardt said.

Nevertheless, there was some disagreement on the committee about the strength of the association between higher hemoglobin and improved quality of life.

The linkage between lower hemoglobin and decreased quality of life hasn’t been firmly established, according to Anthony Murgo, head of early clinical trials development at the National Cancer Institute. He noted three factors are making people feel worse — anemia, chemotherapy and the underlying disease — and that it’s impossible to single out anemia as the single or even the most important contributor to declines in quality of life or fatigue.

Uncertainty about the relationship between hemoglobin targets and benefits is mirrored on the other side of the benefit-risk equation, as Eckhardt noted there are no clear data linking possible adverse events to dose or hemoglobin target.

“We haven’t seen dose-response data on other more negative issues like thrombovascular events, and we don’t know if there is disease promotion and how that relates as you go up the hemoglobin scale,” she said.

The lack of clarity about potential linkages between dose and benefits or risks led ODAC to vote 11-6 against recommending a lower ceiling for hemoglobin levels.

**Getting specific**

The agency also asked ODAC if the data warrant changing ESA labels to state that they are not indicated “for use in the specific tumor types studied in trials that showed adverse safety signals.” Any restrictions “would apply until adequate trials and subsequent data are reviewed by FDA.”

The agency told ODAC that “decreased survival signals were noted in trials enrolling patients with homogeneous tumor types including BEST (breast), ENHANCE (head/neck cancer), and EPO-CAN-20 (NSCLC). Similar signals were also produced in trials that involved heterogeneous tumor types.

FDA’s concerns about specific types of cancer center on tumor promotion, not thrombovascular events, said Pazdur.

He acknowledged the data on specific cancers are “imperfect,” in part because the data were collected in trials that aimed to produce off-label hemoglobin levels. It is this scientific uncertainty that prompted the agency to seek ODAC’s advice.

“Obviously, if we had data that [clearly] indicated a hemoglobin- and disease-related death rate, we wouldn’t be here,” Pazdur said.

Clinicians on ODAC split between those who felt that ESAs should not be given to patients if there are unresolved questions about safety, and those who were leery of making decisions based on trials that can’t be readily extrapolated to approved indications.

Michael Perry, director of the division of hematology/medical oncology at the University of Missouri, said flaws in the design of the BEST breast cancer study, including imbalances in the treatment and placebo arms that could have confounded the results, make it a poor basis for making treatment decisions.

“I would hate to tell people who take care of breast cancer patients they can’t use [an ESA] because of the BEST trial,” said Perry, a permanent ODAC member.

But Silvano Martino, a former ODAC chair who directs the breast cancer program at the Angeles Clinic and Research Institute in Santa Monica, Calif., had no qualms about doing exactly that. “I would love to be able to give FDA my endorsement that you have the right to say to the pharmaceutical companies that you can’t use it in breast cancer,” said Martino, who participated as a temporary voting member.

Otis Brawley, another ODAC alumnus who participated as a temporary voting member, suggested that the absence of solid evidence of harm is not sufficient to allow AMGN and JNJ to market ESAs for breast or other cancers.

“The onus of the law is the opposite; the company has to prove it is safe,” said Brawley, professor of hematology/oncology and medicine at the Emory Winship Cancer Institute in Atlanta. Eckhardt and David Harrington, chair of the department of biostatistics and computational biology at the Dana-Farber Cancer Institute, suggested FDA consult with ODAC again before placing restrictions on use of ESAs in specific tumor types.

Harrington, a permanent member of the committee, said his vote in favor of tumor-specific restrictions was contingent on an
Quality of life

Joanne Mortimer’s reasoning for voting in favor of tumor-specific restrictions touched on one of the biggest disagreements between FDA and ESA manufacturers.

“Why would I treat somebody if I don’t have a compelling reason to think they are getting a benefit from it? There is no clear evidence that quality of life has benefited. I have a hard time not excluding breast cancer patients because I don’t see a benefit to treating them,” said Mortimer, medical director at the Moores Cancer Center at the University of California, San Diego.

AMGN presented summaries of numerous studies that it said demonstrate the positive impact of ESAs on the quality of life of patients with CIA. These included five randomized, placebo-controlled trials that demonstrated improvements in the Functional Assessment of Cancer Therapy (FACT)-Fatigue and the FACT-General instruments.

FACT is widely used in academic clinical trials and cited in the medical literature as a standard quality of life instrument for cancer.

“The benefits of ESAs are clear in clinical practice,” Jeffrey Crawford, chief of medical oncology at Duke University, who spoke as part of AMGN’s presentation to ODAC. “The signs and symptoms of anemia are alleviated, transfusions are reduced, and quality of life is improved.”

FDA was adamant, however, that ESA sponsors have not demonstrated that the drugs improve quality of life for cancer patients. “Based on data provided to FDA, there is no evidence that ESAs improve quality of life or cancer outcomes,” the agency’s briefing document said (see Online Links, A27).

“Improved quality of life, fatigue, and other symptoms associated with anemia have not been established in properly conducted, randomized, double-blind, placebo-controlled studies,” FDA’s Juneja told ODAC.

FDA also is not confident that FACT is a valid instrument, said FDA’s Keegan, but its concerns about AMGN’s and JNJ’s quality of life data for ESAs in cancer are broader; involving trial designs. “We would have liked to see a randomized controlled trial in a homogeneous population, patients who had the same disease, the same stage of disease, and the same type of therapy,” she said.

Rather than quality of life, FDA’s approval of ESAs for CIA is based on their ability to halve the need for red blood cell transfusions. The agency suggested that a decrease in the risks of viral infections from transfusions since Procrit/EpoGen were approved for CIA in 1993, combined with safety concerns that have arisen in the last decade, might prompt ODAC to assess whether their benefits outweigh their risks.

In this instance, committee members rejected FDA’s premise, enumerating a variety of reasons why avoiding transfusions remains an important goal for cancer patients. These included avoiding toxicities that occur with multiple transfusions and the lack of blood supplies and infrastructure to support a major increase in the number of transfusions.

ODAC was more skeptical of AMGN’s and JNJ’s claims that preclinical data demonstrate that ESAs are very unlikely to promote tumor growth.

Roger Perlmutter, EVP of R&D at AMGN, said there are abundant data showing that tumor cells do not have EPO receptors and that “the EPO gene is not involved in tumor growth; it is not an oncogene.”

The picture is not so clear cut, FDA told ODAC. There is evidence of EPO receptors on some types of tumors, an agency scientist said. ODAC members also suggested that ESAs could promote tumor proliferation indirectly, for example by promoting oxygenation of tumors.

“I am concerned this compound is a stimulant” for epithelial tumors, Brawley said. Referring to a popular brand of plant fertilizer, he challenged AMGN to provide data that ESAs “are not Miracle-Gro for cancer.”

Martino called for a stop to all trials of ESAs that seek to achieve off-label hemoglobin levels. “The burning question is does this thing actually kill people in the doses that are reasonable and appropriate,” she said.

FDA also asked the committee if recommendations about duration of use should be added to ESA labels. The agency expressed concern that “when the ESAs are initiated for treatment of chemotherapy-induced anemia, the ESA may be continued when patients are treated with subsequent, less myelosuppressive chemotherapy, including regimens that are unlikely to result in clinically significant rates of anemia.”

ODAC voted 16-1 that the label should “recommend discontinuation of the ESA following completion of a chemotherapy regimen,” and that the use of an ESA should be reevaluated based on the degree of anemia caused by any subsequent treatment.

Next steps

At the outset of last week’s meeting and afterwards in comments to reporters, Pazdur stressed that ODAC’s advice only relates to cancer indications. He declined to provide a timetable for FDA to act on the committee’s recommendations, but noted that any label changes would have to be negotiated with AMGN and JNJ.

That may change this summer, however. Legislation reauthorizing PDUFA is likely to give FDA authority to make label changes without a sponsor’s consent.

The agency plans to hold a meeting of the Cardiovascular and Renal Drugs Advisory Committee in the fall to review the safety of ESAs for renal indications.
## ESA data

FDA convened an ODAC meeting in May 2004 in response to two studies — BEST and ENHANCE — in which head and neck cancer patients who received an erythropoiesis-stimulating agent had lower overall survival and increased tumor progression, respectively. Over the last three years, the agency has received data from four additional studies with signals of decreased survival or tumor promotion in an ESA arm. Most of the data come from studies in which patients were treated to obtain hemoglobin (Hb) levels above the 12 g/dL ceiling on current labels. FDA has received primary data from three of the 13 studies that have been reported since 2004. The trials with negative survival or tumor promotion in an ESA arm are highlighted in color below. The remaining trials did not produce negative survival signals, but FDA cautioned ODAC that the lack of a negative safety signal does not necessarily demonstrate safety. Hazard ratio is a measure of the relative risk of an event occurring; it is used to compare data collected at different times. An HR of 0.5 for overall survival (OS) indicates that the risk of death in one group is half that of the other.

(A) Trials with negative survival or tumor promotion in an ESA arm; CSR=clinical study report; DFS=disease-free survival; PFS=progression-free survival; EFS=event-free survival; HR=hazard ratio; LRC=locoregional control rate; ORR=overall response rate; OS=overall survival; QOL=quality of life; TVE=thrombovascular event; QW=every week; tiW=three times a week; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; Source: FDA briefing document

### Aranesp studies

<table>
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<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Dose &amp; Hb target</th>
<th>Primary endpoint</th>
<th>ESA vs control</th>
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<tbody>
<tr>
<td>20000161 (A)</td>
<td>Lymphoproliferative malignancies receiving chemo; baseline Hb ≤11</td>
<td>Randomized (1:1), double-blind, placebo-controlled trial of pts receiving chemo +/- Aranesp</td>
<td>2.25 µg/kg QW; titrate to maintain Hb &gt;15 (male), &gt;14 (female)</td>
<td>Increase in Hb ≥2 g/dL</td>
<td>OS: HR 1.37 (p=0.037); PFS: HR 1.02 (p=not significant)</td>
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<tr>
<td><strong>Status:</strong> Study closed to accrual; 344 of 340 planned pts; CSR with primary dataset submitted as a component of STN BL 103951/5097; data cut-off 12/05; updated dataset submitted 4/6/07</td>
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<tr>
<td>20010103 (A)</td>
<td>Non-myeloid malignancies not receiving chemo; baseline Hb ≤11</td>
<td>Randomized (1:1:1:9), double-blind, placebo-controlled, multicenter study +/- Aranesp</td>
<td>6.75 µg/kg Q4W; titrate to maintain Hb 12-13</td>
<td>Occurrences of transfusion</td>
<td>Occurrences of transfusion: HR 0.85; OS: HR 1.30 (p=0.008); embolic and thrombotic events, arterial and venous 3.1% vs 1.3%</td>
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<td><strong>Status:</strong> Study closed; 989 of 1000 planned pts; summary data provided in flash report 1/07; primary data submitted 3/07</td>
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<tr>
<td>DAHANCA (SE20029001) (A)</td>
<td>Head and neck cancer; baseline Hb ≤14.5</td>
<td>Multicenter, open-label trial of radiotherapy +/- Aranesp</td>
<td>150 µg QW; titrate to maintain Hb 14.5-15</td>
<td>LRC</td>
<td>3-yr LRC: significant reduction in Aranesp arm (p=0.01); OS: trend towards shorter survival in Aranesp arm (p=0.08)</td>
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<td><strong>Status:</strong> Terminated early by DMC (after 522 of 600 planned pts enrolled) based on lower LRC rates and increased deaths in ESA arm at planned interim analysis; 522 of 600 planned pts; summary results submitted 12/06; CSR anticipated 9/08</td>
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<tr>
<td>20030232</td>
<td>Non-myeloid malignancies receiving chemo; baseline Hb ≤11</td>
<td>Randomized (1:1), double-blind, placebo-controlled</td>
<td>300 µg Q3W; titrate to maintain Hb 12-13</td>
<td>% transfused</td>
<td>% transfused: 24% vs. 41%; OS: HR 0.82 (p=not significant); embolic and thrombotic events, arterial and venous: 7.1% vs. 3.6%.</td>
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<td><strong>Status:</strong> Study closed; 391 of 380 pts enrolled; CSR submitted 4/6/07; primary data submitted 3/07</td>
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<td>GELA LNH 03B (FR20033005)</td>
<td>Diffuse large B cell lymphoma</td>
<td>Open-label, multifactorial design; R-CHOP 14 vs. R-CHOP 21 +/- Aranesp</td>
<td>2.25 µg/kg QW; titrate to maintain Hb 13-15</td>
<td>EFS</td>
<td>Interim analysis 1 yr OS: 78% vs. 70% (p=not significant); interim analysis 1 yr EFS: 73% vs. 64% (p=not significant)</td>
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<td><strong>Status:</strong> Study ongoing; 326 of 600 planned pts enrolled; summary data from interim analysis 12/06 and abstract in 2006; CSR anticipated 9/2010</td>
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### Eprex/Procrit studies

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<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Dose &amp; Hb target</th>
<th>Primary endpoint</th>
<th>ESA vs control</th>
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<tbody>
<tr>
<td>EPO-CAN-20 (A)</td>
<td>NSCLC not receiving chemo; baseline Hb ≤12</td>
<td>Double-blind, placebo-controlled, randomized (1:1) +/- Eprex</td>
<td>40,000 U QW; titerate to maintain Hb 12-14</td>
<td>QOL</td>
<td>QOL: no significant difference; OS: median 63 days vs. 129 days (p=0.04)</td>
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<td><strong>Status:</strong></td>
<td>Terminated early by DSMB for increased deaths in ESA arm; 70 of 300 pts enrolled; results published in abstract in 2004 and in the <em>Journal of Clinical Oncology</em> 3/07</td>
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<tr>
<th>BEST (EPO-INT-76) (A)</th>
<th>Metastatic breast cancer</th>
<th>Randomized, double-blind, placebo-controlled</th>
<th>Dose adjusted to achieve and maintain Hb 12-14</th>
<th>1-yr OS</th>
<th>1-yr OS: 70% vs. 76%, (p=0.0117, HR 1.359); all-cause deaths at 4 months after randomization: 41 vs. 16 deaths; time to disease progression, PFS and ORR were not significantly different between the 2 groups</th>
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| Status:              | Terminated in April 2002, after review of data in the first 938 pts by the DMC, due to evidence of excess mortality in the Eprex arm |

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<tr>
<th>AGO/NOGO</th>
<th>Cervical cancer; baseline Hb not specified</th>
<th>Open-label, randomized (1:1), chemo/radiation +/- Eprex</th>
<th>10,000 U tiW; titerate to maintain Hb 13</th>
<th>5-yr DFS</th>
<th>5-yr DFS: results not provided; 2-yr recurrence rate: 17% vs. 25% (p=0.074)</th>
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| Status:              | Accrual completed; 264 of 264 planned pts; results published in abstract in 2003; summary results provided 4/06 |

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<tr>
<th>EPO-CAN-17</th>
<th>Stages I-IV breast cancer; baseline Hb ≤15</th>
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<th>40,000 U QW; titerate to maintain Hb 12-14</th>
<th>QOL</th>
<th>Kaplan Meier estimates of survival curves similar (p=0.82 log rank test); ORR (stage 4 pts only): 37% vs. 30% (p=not significant); TVE: 20.5% vs. 16.9%</th>
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| Status:              | Accrual completed; 354 of 350 pts; results published in *Journal of Clinical Oncology* 4/05; summary results provided 4/06; limited safety datasets provided 3/07 |

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<th>10,000 U tiW for Hb &lt;12.5; 4,000 U tiW for Hb ≥12.5; titerate to maintain Hb 12.5-15</th>
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| Status:              | Terminated early for poor accrual; 301 of 800 pts enrolled; results provided 4/06; CSR expected ~12/07 |

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<th>40,000 U QW; titerate to maintain Hb 12-13</th>
<th>2-yr OS</th>
<th>2-yr OS: no results provided; OS: median 338 vs 299 days; ORR 55% vs. 47%; TVE 17.7% vs. 8.5% (p=0.097)</th>
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| Status:              | Terminated early for poor accrual; 389 of 612 pts enrolled; results published in abstract in 2003, summary results provided 4/06; CSR expected 2/08 |

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### ESA Data, from previous page

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**Status:** Accrual completed; 593 of 593 planned pts; results based on unpublished data in 2007; summary results provided 4/06

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<td>2-yr LRC</td>
<td>1-yr LRC: 63% vs. 70% (HR 1.18, p= not significant); 1-yr OS: 70% vs. 81% (HR 1.57); ORR: 73% vs. 75%</td>
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**Status:** Terminated early by DSMB for trend to poorer LRC and OS in EPO arm; 148 of 372 pts enrolled; results published in abstract in 2004

### NeoRecomon study

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<td>NeoRecomon/placebo dose adjusted to achieve patients (HR 1.62; and maintain Hb 14.5 (female), 15 (male)</td>
<td>Locoregional PFS</td>
<td>Shorter locoregional PFS in NeoRecomon p=0.0008; shorter time-to-locoregional progression in NeoRecomon patients (HR 1.69, p=0.007); shorter OS in NeoRecomon patients (HR 1.39; p=0.02)</td>
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**Status:** Enrolled 351 pts undergoing treatment with either definitive radiotherapy or postoperative radiotherapy between March 1997 and April 2001

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### BioCentury Company Index

**May 14, 2007**

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FDA advisory committee meetings usually revolve around interpretations of data presented in briefing documents or articles from peer reviewed journals, but the discussion at last week’s Oncologic Drugs Advisory Committee meeting on erythropoiesis-stimulating agents was heavily colored by TV advertisements and newspaper reports of impropriety in the marketing of ESAs.

Otis Brawley diverted the meeting onto the topic of media criticism by chastising Johnson & Johnson’s television advertisements that purported to show cancer patients leading vigorous lives and attributing their energy levels to the company’s Procrit epoetin alfa.

“Most doctors and most patients think this drug has been approved because it improves quality of life — it improves fatigue,” said Brawley, who served as a temporary voting member of ODAC. “I don’t see that on the FDA indication. I see it on late night television. There is a lot of sleight of hand here on what the drug is used for and what it is approved for.”

Brawley, a professor of hematology/oncology and medicine at Winship Cancer Institute in Atlanta, Ga., is a former permanent member of the committee.

Other committee members asked why FDA allowed JNJ (New Brunswick, N.J.) to broadcast the ads, because the Procrit label does not include quality of life claims (see Cover Story).

“The problem has been that physicians have been sold the conceit, rightly or wrongly, that in fact quality of life is very much improved when you use these agents,” said Silvano Martino, director of the breast cancer program at the Angeles Clinic and Research Institute in Santa Monica, Calif.

Helen Schiff, the voting patient representative at the ESA meeting, called on FDA to compel JNJ to run corrective advertisements.

“Unfortunately, I think we have to combat a campaign that set the wrong tone for the doctors and patients,” said Schiff, who called for “corrective ads that say that what was said in the past was wrong. We have to get patients re-educated.”

Richard Pazdur, director of FDA’s Office of Oncology Drug Products, said he agreed with ODAC’s criticism of the agency.

“Advertising claims are supposed to be derived from product labeling. Obviously there is a great deal of concern that I have and the clinical review staff have about the advertising claims that were made” for Procrit, Pazdur told the committee.

The clinical review staff is not responsible for enforcement of FDA regulations that are intended to preclude false and misleading advertising, Pazdur noted. The agency’s enforcement staff has “a great deal of discretion” and needs to consider the “fine line between First Amendment speech and protection of the American people from false and misleading advertisements.”

Nonetheless, Pazdur said, “the FDA is responsible for giving the public as well as the review staff the reason for why these ads were allowed to continue.”

After the meeting, a JNJ spokesperson challenged Pazdur’s and ODAC members’ assertions that the Procrit label did not support advertisements touting the drug’s ability to relieve fatigue and other anemia symptoms caused by chemotherapy.

“It is important to note that patient information in our FDA-approved label prior to the March 9, 2007, ESA class label change contained information relating to the signs and symptoms of anemia,” Stephanie Fagan, senior director of corporate communications for JNJ’s Ortho Biotech division, told BioCentury.

Until March 2007, the FDA-approved label stated: “Procrit is used to treat anemia (a lower than normal number of oxygen-carrying red blood cells). People with anemia may feel tired or may feel a lack of energy. They may also experience weakness, dizziness, difficulty with concentration, shortness of breath, chest pain, and feeling cold all of the time. Your doctor has prescribed Procrit to treat your anemia. If your body responds to Procrit, your symptoms may improve.”

Brawley also noted the media controversy over allegations that physicians have received financial inducements to administer Procrit. ESAs might be over-used, and patient safety compromised, because of attempts by physicians to maximize their revenues, he suggested.

“The doctors get about $1,200 for every dose they give patients,” Brawley said.

Pending litigation filed against JNJ in the U.S. District Court for the District of Massachusetts accuses the company of providing physicians with thousands of vouchers for $1,000 discounts on Procrit. The suit, filed under the Federal Civil False Claims Act by Mark Duxbury, a former JNJ salesperson, charges that the company then helped the physicians bill Medicare for Procrit they obtained with the vouchers.

JNJ does not comment on pending litigation, said Fagan, who did tell BioCentury in March that the company has paid financial incentives for prescribing Procrit. At the time, she said its practices are “consistent with federal government regulations” (see BioCentury Extra, Wednesday, March 21).

Amgen Inc. (AMGN, Thousand Oaks, Calif.) has never marketed Aranesp or Epogen to consumers, nor has it provided financial incentives to physicians for prescribing the drugs or any other product, company spokesperson David Polk told BioCentury in March.
Regulation

A roll of the dice

By Michael Flanagan
Staff Writer

There may be better days to come for the cancer immunotherapy space, but last Wednesday was not one of them. The Oncologic Drugs Advisory Committee’s thumbs-down for IDM Pharma Inc.’s Junovan mifamurtide for osteosarcoma and the approvable letter for Dendreon Corp.’s Provenge sipuleucel-T prostate cancer vaccine underlined that FDA is in no mood to relax its demand for well-designed trials that meet their primary endpoint.

Indeed, the Junovan panel, which voted 12-2 that IDM failed to demonstrate substantial evidence of efficacy, is a reminder that asking for approval based on a non-registration study is a roll of the dice, at best.

Junovan and Provenge are two of the first in a wave of cancer immunotherapies moving through the clinic that act by stimulating the immune system to reject or destroy tumor cells.

For IDMI (San Diego, Calif.), ODAC’s issues related mainly to flaws in the design of the trial used to support the company’s efficacy claim for Junovan, a liposomal formulation of muramyl tripeptide phosphatidyl ethanolamine that works by stimulating tumoricidal activity by macrophages. This may come as no surprise, given that the data package was based on pooled analyses of data from a single cooperative trial that began in 1993.

The early preclinical and clinical work on Junovan was conducted by Ciba-Geigy Corp., a predecessor of Novartis AG (NVS; SWX:NOVN, Basel, Switzerland), under an IND originally submitted in 1988. However, the pharma company dropped the program in 1996 after deciding that the osteosarcoma market would be too small to justify its R&D costs. Junovan was picked up by Jenner Biotherapies Inc., which subsequently went out of business and sold the program to IDMI in 2003 — long after the clinical trial supporting the NDA had completed enrolling patients.

While the IND was changing hands, a pediatric cooperative group called Children’s Oncology Group began an open-label Phase III trial (Study INT-0133) that enrolled 678 patients with resectable, non-metastatic, high-grade osteosarcoma. It was by far the largest study ever conducted in a patient population where only 400 cases are diagnosed each year in the U.S.

The trial was never meant for registration purposes. While it was powered to measure disease-free survival, DFS was not clearly defined as the primary endpoint, although the company and FDA both agreed during pre-NDA meetings that it could be inferred as such from the protocol.

Another complication was the factorial design of the trial, which consisted of four arms: what FDA considered the “standard regimen” for osteosarcoma of high-dose methotrexate, cisplatin and doxorubicin; the standard regimen plus either Junovan or the chemotherapeutic ifosfamide; and the standard regimen plus both Junovan and ifosfamide.

IDMI decided the best way to analyze the complex dataset would be to pool the results of the two arms that had received Junovan and compare that to pooled data from the other two arms. Using this method, IDMI concluded that Junovan significantly increased DFS, as patients receiving it showed a 24% decrease in risk of relapse, progressive disease or death (p=0.0245).

However, the company believed the most compelling argument supporting the approval of Junovan was overall survival, which it said could be inferred as a secondary endpoint based on INT-0133’s intent to “improve survival of patients with osteogenic sarcoma,” as described in the protocol. On this measure, IDMI determined that Junovan provided a significant survival benefit in comparison to pooled data from the non-Junovan regimens. In fact, the 6-year survival probability was 77% for patients receiving the immunotherapy and 66% for those not given Junovan.

Based on the strength of these pooled analyses, IDMI argued that Junovan provided a sufficiently compelling benefit to merit approval in an Orphan indication like osteosarcoma; the company submitted an NDA to FDA and an MAA to the EMEA for Junovan (Mepact in Europe) last year.

However, FDA made clear from the start that it took a different view. In its briefing documents, the agency said that IDMI “failed to demonstrate that their product, mifamurtide (MTP-PE), provides substantial evidence of efficacy.”

The agency focused on the integrity of the dataset. An approvable letter for Dendreon Corp.’s Provenge (Mepact in Europe) was issued by the Oncologic Drugs Advisory Committee’s last meeting, but a final decision was delayed pending the agency’s review of new data it had received.

‘You go to the FDA with the data set you have, not the data set you wish you had.’
— Peter Adamson of Children’s Hospital of Philadelphia

FDA disagreed with IDM Pharma’s analysis that Junovan met the primary endpoint of disease-free survival (DFS), defined as the time from randomization to relapse of osteosarcoma or death, in the Phase III INT-0133 study conducted by the Children’s Oncology Group. IDMI argued there was a 24% reduction in the risk of relapse, progressive disease or death in patients given Junovan (hazard ratio=0.76) compared to those on regimen A (methotrexate, doxorubicin and cisplatin) or regimen B (regimen A plus ifosfamide) (hazard ratio=1).

FDA’s analysis, which included modifications to the DFS data and excluded patients not considered to be part of the intent-to-treat population, raised the hazard ratio from 0.76 to 0.78, with the p-value changing from 0.025 to 0.065. The results were even worse when the agency excluded the 10% of patients who received induction chemotherapy but never entered the maintenance phase, when they would either receive chemo alone, or have Junvan added to their treatment. Source: IDM & FDA

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<tr>
<th>IDM analysis</th>
<th>Hazard ratio</th>
<th>P-value</th>
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<tr>
<td>Junovan plus A/B vs. A/B</td>
<td>0.76</td>
<td>0.025</td>
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<th>FDA analysis</th>
<th>Hazard ratio</th>
<th>P-value</th>
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<tr>
<td>Junovan plus A vs. A</td>
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<td>0.960</td>
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<tr>
<td>Junovan plus B vs. B</td>
<td>0.62</td>
<td>0.010</td>
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<tr>
<td>FDA’s integrated analysis</td>
<td>0.78</td>
<td>0.065</td>
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A reviewer identified 66 discrepancies between DFS events used by the company and those the agency came up with based on its own examination of the case report forms. After modifying these data points and removing patients deemed ineligible by enrollment criteria, FDA’s analysis was that Junovan had not significantly improved DFS (see “Junovan Filters,” A10).

Another set of issues arose from the design of INT-0133, which called for all patients to receive induction chemotherapy for 10 days prior to surgical resection, followed by a maintenance phase of chemotherapy when the experimental agents would be administered for the first time. But randomization occurred at the time of enrollment, and substantially more of the patients who dropped out before reaching the maintenance phase because of DFS events or death had been randomized to non-Junovan arms.

IDMI’s calculations included the dropouts, which accounted for 10% of total patients in the trial, but FDA decided they should be thrown out. Removing these patients also led to Junovan failing to meet the DFS endpoint.

According to the agency’s briefing documents, “These events are not attributable to regimen assignment and represent statistically ‘noise’ occurring before the possible initiation of MTP-PE administration that by chance favored the MTP-PE containing arms” (see Online Links, A27).

In addition, FDA argued that it was inappropriate for IDMI to have pooled data from an “experimental arm” (standard plus ifosfamide) that ended up faring worse than standard alone.

According to Michael Perry, director of the division of hematology/medical oncology at the University of Missouri and a member of ODAC, the agency’s assessment that Junovan’s failure to improve DFS versus the standard arm was an important observation. Quite simply, Junovan “did not add anything,” he said.

According to David Harrington, professor of biostatistics and computational biology at the Dana-Farber Cancer Institute and a voting member of ODAC, the key information resulting from the INT-0133 trial came from comparing the standard regimen versus standard plus Junovan, which produced similar results. “In general, I do not favor pooled analyses,” he added. Harrington voted no.

“You go to the FDA with the data set you have, not the data set you wish you had,” said Peter Adamson. “If this was a huge advance, we wouldn’t be struggling; nevertheless, we have not had an advance in this area in 20 years so we can’t simply dismiss an incremental advance, if it is there.”

Adamson, who didn’t find what he was looking for and voted no, serves as chief of the division of clinical pharmacology at the Children’s Hospital of Philadelphia and was a temporary voting member on the panel.

Paul Meyers, vice chair of Pediatrics at Memorial Sloan-Kettering Cancer Center and a principal investigator on the INT-0133 study, countered that ifosfamide is actually considered to be part of a standard regimen in several European countries and that “there is no such thing as a standard of care for treating osteosarcoma.”

Lee Helman, scientific director for clinical research at the National Cancer Institute and a temporary voting member on ODAC, who voted “no,” questioned why more of the discrepancies between sponsor and agency had not been cleared up in the 10 years since the last patient was enrolled in Study-0133.

Helman then raised the possibility of additional studies to clarify Junovan’s efficacy, to which Meyers suggested there is little chance of ever running a trial as large as Study INT-0133 again, given the few new cases diagnosed each year.

Bonnie Mills, VP of clinical operations at IDMI, told the committee that the reason the company had not conducted any trials since licensing the program in 2003 is because there have been some manufacturing issues and no study material has been available. However, the company did recently start a smaller study that is planned to enroll osteosarcoma patients with metastatic disease. Junovan’s PDUFA date is in late August.

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Cancer immunotherapy milestones

In April, Dendreon’s Provenge sipuleucel-T became the first cancer vaccine to be discussed by an FDA advisory committee, while Junovan mifamurtide from IDM Pharma Inc. had a panel meeting of its own last week. Late-stage data for three more candidates are anticipated by year end. (A) Reported data on the secondary endpoint in late 2006.

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Indication</th>
<th>Status/milestone</th>
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<tbody>
<tr>
<td>Cell Genesys</td>
<td>GVAX for prostate cancer</td>
<td>Metastatic hormone-refractory prostate cancer (HRPC)</td>
<td>Complete Ph III enrollment mid-07</td>
</tr>
<tr>
<td>Coley/ Pfizer</td>
<td>CPG 70/9 (PF-3512676)</td>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>Completed Ph III enrollment</td>
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<td>Dendreon</td>
<td>Provenge sipuleucel-T</td>
<td>Androgen-independent prostate cancer (AIPC)</td>
<td>FDA approvable letter</td>
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<td>FaviD</td>
<td>Follicular NHL</td>
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<td>Genitope</td>
<td>MyVax (GTOP-99)</td>
<td>Follicular NHL</td>
<td>Ph III data YE07</td>
</tr>
<tr>
<td>IDM Pharma</td>
<td>Junovan mifamurtide</td>
<td>High-grade osteosarcoma</td>
<td>FDA decision late August; under review in EU</td>
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<tr>
<td>ViRexx/ United Therapeutics</td>
<td>OvaRex</td>
<td>Ovarian cancer</td>
<td>Ph III data 2H07</td>
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Junovan vs. Provenge

Both IDMI and DNDN (Seattle, Wash.) focused their arguments for approval on post hoc analyses that suggested their respective agents demonstrated a survival advantage, which each company had hoped would be sufficiently compelling to overcome other flaws in their applications.

In retrospect, ODAC’s negative opinion on Junovan could represent exactly the result one might have expected had that committee been assigned to review Provenge. DNDN’s case for Provenge, an autologous dendritic cell therapy that stimulates an antigen-specific immune response against prostatic acid phosphatase (PAP), was similar to IDMI in that the company was relying on data dredging to support its efficacy claim.

Both Phase III studies of Provenge (D9901 and D9902A) missed the primary endpoint of time to disease progression in patients with androgen-independent prostate cancer. But a post hoc analysis of the survival data in Study D9901 showed the vaccine led to significantly greater median survival than placebo. A trend to longer survival in Study D9902A was not statistically significant, but a pooled analysis yielded a significant result.

Unlike Junovan, the BLA for Provenge was instead brought before CBER’s Cellular, Tissue and Gene Therapies Advisory Committee, which voted 13-4 that DNDN had provided substantial evidence of efficacy in asymptomatic, metastatic, androgen-independent prostate cancer (see BioCentury, April 2).

But just as ODAC was preparing to discuss Junovan, FDA issued an approvable letter for Provenge in which the agency asked for an additional clinical trial.

A number of patient advocacy organizations immediately protested the agency’s snub of its panel. For example, Malecare, a prostate cancer support group, posted an open letter on its website addressed to FDA, stating: “The recent failure of the FDA to approve the license for Provenge has stunned the prostate cancer community.”

“We call upon you, the FDA, to reconsider your position. We are terminally ill, we are going to die and we don’t have enough options. We want to determine the course of our lives by altering the course of our disease. Please do not deny us,” it concluded. Readers were encouraged to attach their name to the letter, which is to be sent to the agency on May 18.

On Friday, FDA sent a statement to BioCentury regarding the agency’s decision not to follow the advice of its CBER committee. In it, the agency noted that several members of the committee had raised issues about the strength of the data used to support the efficacy of Provenge.

The statement concluded FDA shares the goal of bringing novel products to approval, “as soon as they are shown to be safe and effective.”

John Longenecker, president and CEO of Favrille (FVRL, San Diego, Calif.), cautioned against reading too much into last week’s events. “I think there is a tendency towards overreaction,” he said. “There may be a tendency to feel that the agency has gone conservative or that it’s more difficult, but I think that’s an overreaction as cases will need to be judged on their relative merits.”

Longenecker noted the cases for both Junovan and Provenge “were a bit unusual from a regulatory standpoint because they were based on post hoc analyses or missed primary endpoints, so they could have been seen as maybe a bit of a reach.”

He added: “These situations are both outside of the norm in terms of regulatory filings and analysis of data.”

FVRL’s FavID is a tumor-specific idiotype protein conjugated to KLH immunostimulatory protein that is in Phase III testing for non-Hodgkin’s lymphoma (NHL). The company hopes to report data by year end, though the trial’s time-to-progression endpoint is event-driven. Longenecker does hope to be in a position to submit a BLA for FavID in 2008 (see “Cancer Immunotherapy Milestones,” A11).
Strategy

Bigger platform for product deals

By Alexei Ku
Staff Writer

When Peptech Ltd. got a cool $141 million in January as a result of its investment in Domantis Ltd., which GlaxoSmithKline plc acquired, the Australian company said it planned to use the money to make the transition from a research play to a biologics story with clinical development capabilities. To move quickly, Peptech hoped to acquire companies or clinical stage molecules. But with a picked-over landscape, that has proved easier said than done.

In the interim, Peptech is beefing up its internal antibody platform, which it reckons should allow it to pursue organic growth and make it a more attractive suitor. Last week, it acquired EvoGenix Ltd., which has complementary antibody technology.

Peptech (ASX:PTD; LSE:PTDX, North Ryde, Australia) will pay A$20.9 million in cash, plus another A$135.1 in stock, to buy EvoGenix (ASX:EGX, Sydney, Australia), for a total of A$156 million ($128.1 million).

EGX has only discovery stage and preclinical compounds in its pipeline, but it adds Superhumanisation and EvoGene optimization technologies to PTD’s suite of antibody engineering technologies. Both companies say the EGX technologies will complement PTD’s own Synhumanisation platform.

Synhumanisation works by attaching mouse binding domains to antibody frameworks from New World primates. Such frameworks are human-like, but not similar enough to human antibodies to violate patents surrounding human or humanized antibodies to a given target.

EGX’s Superhumanisation technology humanizes mouse antibodies, while EvoGene further optimizes antibodies after humanization to increase targeting activity and specificity.

Thus, PTD CEO John Chiplin said, the companies’ platforms dovetail in their ability to produce antibodies for targets with varying levels of IP coverage. Depending on the IP on a given target, one or the other platform would be more attractive.

“If there’s a novel target that has not been dominated by other companies, then Superhumanisation is the way to go,” he told BioCentury. But in cases such as the anti-TNF space, which is dominated by several companies, “then you need to use Synhumanisation. It depends on the IP landscape around the target.”

PTD still intends to acquire clinical programs in mid- to late-stage development but has had difficulties finding programs worth acquiring. “There are not a lot of those types of assets on a worldwide basis,” Chiplin said. “We talked to the U.S. and European biologics companies that are still around, but the independent antibody universe is rapidly declining.”

Given the scarcity of later-stage compounds, Chiplin said he would be willing to acquire individual antibody programs in earlier stages of development.

“In antibodies, everybody is going further back — investing in early-stage assets — than they would like,” he said. “One of the reasons that we could do this is that if we go early-stage, we know that we have the funds to develop antibodies into Phase I and Phase II testing.”

One of PTD’s goals will be to build U.S. operations, which focus on identifying and managing product acquisition opportunities. EGX will fit into this leg of the strategy via its operations in Mountain View, Calif., which the company picked up in its 2005 acquisition of antibody engineering company Absalus Inc. (see BioCentury, April 11, 2005).

Chiplin believes PTD will have time to browse, as the combined cash of A$175 million ($143.7 million) should last for two to three years. The newco’s market cap will be about A$470 million ($386.1 million).

“We’ve done our math, and a return to the capital markets is highly unlikely before the 2009-10 time frame, when some of our clinical programs will be ramping up,” he said.

The combined company has 12 programs in development, including five from EGX and seven from PTD. EGX CEO Merilyn Sleigh, who will assume a senior advisory role at PTD, said four are expected to enter the clinic over three to four years, and the rest would be out-licensed in the preclinical stage.

By 2009, PTD hopes to have at least one candidate each in Phase I, II and III trials, as well as two partnered compounds. Chiplin hopes to begin partnering next year.

PTD’s lead program is PN0621, a domain antibody against TNF for rheumatoid arthritis (RA), psoriatic arthritis, Crohn’s disease, irritable bowel syndrome (IBS) and ankylosing spondylitis. Phase I testing is slated to start this month.

EGX’s EGX 010, a modified version of osteoprotegerin, is expected to enter Phase I testing for bone loss and bone cancer in 2008.

PTD is still seeking to divest its two marketed animal health products, Superlorin and Ovuplant.
**Product Development**

**Silencing a silent killer**

By Urooj Mujtaba  
Staff Writer

Proprotein convertase subtilisin/kexin type 9 was linked to autosomal dominant hypercholesterolemia as early as 1999, but the specific cellular substrate of the enzyme is unknown. This challenge may make a gene silencing approach attractive, a hypothesis that will be tested under last week’s deal between Isis Pharmaceuticals Inc. and Bristol-Myers Squibb Co. to discover, develop and commercialize antisense compounds targeting PCSK9 to prevent and treat cardiovascular disease.

PCSK9 is a protease that degrades specific cellular components and helps regulate the level of cholesterol in the bloodstream. People with excessive PCSK9 have high levels of LDL cholesterol, whereas those with mutations that reduce the levels of PCSK9 have lowered LDL cholesterol and reduced risk of coronary artery disease, with normal liver function.

“Our work and that done by others demonstrates that PCSK9 contributes to the degradation of LDL receptors. When you reduce PCSK9, you end up with increased levels of LDL receptor expression and therefore lower LDL cholesterol levels in the bloodstream,” said Kate Corcoran, VP of corporate development at ISIS.

According to ISIS, companies working on small molecule discovery programs involving PCSK9 may be running into roadblocks because the enzyme’s substrate is not known. But using antisense, said Corcoran, “all you need to know is the gene sequence, because we interfere with the production of the protein rather than with the activity of the protein. It’s extremely straightforward to make an antisense drug candidate even against targets that have unknown activity.”

ISIS’s second-generation antisense compounds bind to their target RNA and activate the cellular enzyme RNase H, which then destroys the target RNA, inhibiting production of a specific protein, according to Corcoran.

BMY (New York, N.Y.) will have exclusive, worldwide rights to products from ISIS’s PCSK9 research program, which includes an undisclosed number of compounds. The biotech did not provide a specific timeline for when it expects the first compound to begin preclinical or clinical testing.

ISIS (Carlsbad, Calif.) will receive $15 million up front and at least $9 million in research funding over a three-year period. It is eligible for $168 million in milestones for the first candidate and additional milestones for follow-on compounds, plus royalties in the high single-digit to low double-digit range. The partners will share preclinical development responsibilities, and BMY will be responsible for clinical development and commercialization.

A competitive program is from Alnylam Pharmaceuticals Inc. (ALNY, Cambridge, Mass.), which last year reported preclinical data on an siRNA that silenced the PCSK9 gene in a mouse model of hypercholesterolemia and reduced cholesterol levels.

President and CEO John Maraganore said he thinks one of the attractive attributes of ALNY’s molecules is their pharmacology. “We’re able to see very rapid onset of action — we see a durable effect even with a single injection,” he said.

ALNY’s program is not currently available for global partnering. “We have no desire to partner our program, at least not in the U.S. right now — we won’t look to partner it until there’s a lot more value,” Maraganore told BioCentury. “One of the attractive things about the target is that you can establish clinical proof of concept relatively early in development. Even in a Phase I trial you’ll be able to show cholesterol reduction.”

Corcoran said ISIS partnered its program early “because the valuation was so attractive and Bristol was so motivated to move it along quickly. There’s a lot of work that needs to be done to get to a clinical candidate and our cardiovascular focus right now is on 301012.”

ISIS 301012 is in Phase II testing to treat hypercholesterolemia. The company plans to begin its familial hypercholesterolemia registration studies this year, and it intends to partner the compound prior to starting the Phase III studies for the routine high cholesterol patient population. The compound targets apolipoprotein B-100 (Apo B-100).
ALS: Sodden dance

By Michael Flanagan
Staff Writer

While it has been known for some time that a mutation in the superoxide dismutase 1 gene plays a role in some cases of amyotrophic lateral sclerosis, just how it works has been a mystery. A pair of articles published in Nature Neuroscience last month point an accusatory finger at glial cells with mutant SOD1 in the degeneration of neurons associated with the disease.

One group uncovered an SOD1-mediated pathway associated with neurotoxicity, while the other described an embryonic stem cell-based model that could be useful for screening ALS candidates.

Last week, a third group published a paper in Nature Medicine describing the design of an antibody that recognizes only misfolded forms of SOD1, which they say can be used as a tool for further study of ALS.

The progressive neurodegenerative disease is characterized by the deterioration of motor neurons in the brain and spinal cord that leads to loss of motor control, muscular atrophy and eventually death. Addressing the disease pharmacologically has proven difficult, as most cases are sporadic, meaning the patient has no familial history of the disease and it can’t be linked to any particular genetic defect.

According to Serge Przedborski, professor of neurology and pathology at Columbia University and an author on one of the studies, SOD1 is one of the only known genetic mutations that has proven useful for studying ALS. “About 10% of ALS patients will clearly have a positive family story for the disease, and about 25% of them will carry an SOD1 mutation,” he said.

But while transgenic mice expressing mutant SOD1 develop an ALS-like phenotype, the neurotoxic mechanism and site of action have remained a mystery.

The two studies in Nature Neuroscience suggest an important role for astrocytes, a subtype of glial cells that were long thought of as providing little more than structural and metabolic support for brain cells. “For many years, the only association between astrocytes and ALS was a single finding that these cells may not properly take up glutamate, leading to excitotoxicity,” said Przedborski.

Przedborski’s group showed that SOD1-mutant astrocytes appear to exert neurotoxic effect by releasing soluble factors when co-cultured with spinal primary and stem cell-derived motor neurons. The group also showed that other types of similarly mutated cells present in the CNS, such as fibroblasts, microglia, cortical neurons and myocytes, did not cause similar neurotoxicity.

While the group was not able to identify the toxic factor or factors released by the astrocytes, it did find that their neurotoxicity was dependent on the activation of a pathway involving Bax, a pro-apoptotic member of the Bcl-2 protein family.

In addition to further elucidating the link between astrocytes and Bax activation, Przedborski said his group “plans to generate physical information about the toxic factor, such as size and structure, which won’t tell us exactly what it is, but it will help narrow down the search.”

In the second Nature Neuroscience study, a group from Harvard University used embryonic stem cells (ESCs) bearing mutant SOD1 genes to derive motor neurons that displayed characteristics commonly associated with ALS. Tom Maniatis, professor of molecular and cellular biology at Harvard and a study author, told BioCentury the study “establishes, in principle, the possibility of using stem cells to study disease mechanisms using the genes of affected individuals.”

He added: “By studying motor neurons derived from these embryonic stem cells, it may be possible to identify disease mechanisms. These cells may also be used to screen for small molecules that prevent disease progression ex vivo.”

In addition to further isolating toxic factors and characterizing mutant glia, the group hopes to develop high throughput screens to identify compounds that counter glial effect or spare motor neurons.

In the Nature Medicine paper, scientists from the University of Toronto and colleagues sought to study another proposed toxic factor in ALS — misfolded versions of the SOD1 protein itself. They used high-resolution X-ray crystallography to design an antibody specific for an epitope of SOD1 that is normally buried in the native dimer interface of the protein and thus is accessible only in conformations in which the dimer is disrupted or misfolded.

Using their SEDI (SOD1 exposed dimer interface) antibody, the researchers showed the presence of misfolded SOD1 in three mouse models of ALS and in a human ALS patient with mutated SOD1. They further showed in the mice that misfolded SOD1 appeared before symptom onset and decreased at the end stage of the disease, which they attributed to the loss of motor neurons.

Although further research is needed to correlate disease progression with levels of misfolded SOD1, the authors suggested the SEDI antibody might make it possible to follow the disease’s course using cerebrospinal fluid or other samples, and could even have diagnostic or therapeutic uses.

They said the antibody will be made available for research.

The first two studies “clearly demonstrate what has been suspected for some time: that ALS is a non-cell autonomous disease. The development of ALS involves a complex interplay between distinct cell types, which include motor neurons, astrocytes and microglia,” said Warren Huff, president and CEO of Reata Pharmaceuticals Inc. (Dallas, Texas).

Indeed, the group from Columbia found that while Bax inhibition protected against astrocyte-mediated motor neuron death, it did little to improve survival in transgenic mutant SOD1 mice. As a result, Przedborski said further research will be necessary to elucidate what other factors contribute to in vivo motor neuron damage.

Huff noted that because the presence of mutant SOD1 in just one cell type will...
Terpene assembly line

By Alexei Ku
Staff Writer

Terpenoids are a class of plant secondary metabolites that include some important pharmacologically active compounds, but they are produced in low concentrations in plants and are expensive to produce synthetically. Researchers from the University of California at Berkeley have figured out how to retool the metabolic pathways of E. coli to produce functional plant-derived terpenoids at high concentration, which could significantly reduce the cost of manufacturing compared with existing synthetic and extractive techniques.

In Nature Chemical Biology, the group described a process in which they pieced together endogenous bacterial genes with genes imported from plants or yeast to assemble the basic elements of two pathways to produce functionalized hydroxycadinene and artemisinic acid. Hydroxycadinene is a semi-synthetic precursor to the terpene gossypol and artemisinic acid is the precursor to the malaria drug artemisinin. Gossypol was originally developed in China as a contraceptive, but development was discontinued due to the dehydrogenase inhibitor’s adverse effects.

Though researchers have made several attempts to engineer functional terpenoid production into E. coli, none have been able to clear the biochemical hurdles posed by the requirement for a group of membrane-bound heme monooxygenases called the cytochrome P450 superfamily. P450s, which don’t naturally occur in E. coli, are one of the most important classes of enzymes in the biochemical assembly of terpenes, as well as several other plant-derived compounds. They are responsible for catalyzing eight of the roughly 20 steps involved in the synthesis of the terpenoid paclitaxel, which is used to treat cancer.

The issue is that the expression of P450 genes in E. coli often results in folding and translation problems, as well as difficulties due to membrane insertion, cofactor incorporation, post-translational modification and association with protein partners.

The researchers were able to overcome these limitations with chemical engineering tricks such as codon optimization and N-terminal transmembrane modification to generate hybrid constructs of the enzymes that were sufficient to catalyze the reactions necessary to yield terpenoid precursors inside the E. coli system.

The researchers then mixed and matched expression vectors and redox partners to optimize the system’s yield, and in this stepwise fashion gradually increased the productivity of each pathway, ultimately leading to the fabrication of complex sesquiterpenoids at concentrations of >100 mg/L. According to Michelle Chang, a post doc fellow at UC Berkeley and an author of the paper, conventional methods of sesquiterpenoid production on average can yield 5 mg/L using equivalent resources and time.

But Chang also told BioCentury the process of implementing her team’s procedure on an industrial scale would be quite slow, as the environmental conditions necessary to stabilize the enzyme hybrids, such as very low temperatures, might be difficult to meet on a larger scale.

She added that while artemisinin and gossypol are assembled with relatively few chemical alterations, other therapeutically-valuable terpenes often require much more complex biochemistry.

Amyris Biotechnologies Inc. (Emeryville, Calif.) has a royalty-free license to the technique specifically for artemisinin. It is using the process to develop a platform to manufacture the drug in collaboration both with UC Berkeley and The Institute for OneWorld Health (San Francisco, Calif.), a non-profit drug development company that also has a royalty-free license to the technology.

In 2004, OneWorld received a $42.6 million, five-year grant from the Bill & Melinda Gates Foundation to develop a platform for artemisinin and its derivatives under the license. The non-profit is using a portion of the award to sponsor research and development at UC Berkeley and Amyris.

The university team is doing the front-end research, while Amyris is involved in process development. OneWorld is developing the commercial plan for engaging pharmaceutical companies to manufacture microbially derived artemisinin and integrate the source into artemisinin-based combination therapies (ACTs).

Taxol paclitaxel is marketed by Bristol-Myers Squibb Co. (BMY, New York, N.Y.).

likely turn out to be insufficient for disease development, drug discovery assays must be designed to anticipate and investigate such interactions and dependencies.

“It would be appropriate to develop and execute high throughput screens aimed at identifying small molecules that impact the processes revealed by these studies, such as the secretion of the so-called toxic factors,” he said.

Reata’s RTA 801 is an SOD1 reactivator that has shown potential to cross the blood-brain barrier and biochemically stabilize misfolded SOD1 in preclinical models. The company hopes to file an IND for the small molecule in 2008.
Emerging Company Profile

Complex Bio: Finding a peg that fits

By Christopher Maggos
Senior Writer

Pegylation can improve the half-life of protein therapeutics but can be difficult to implement for peptides and small proteins because it alters the pharmacokinetics of the molecules. Complex Biosystems GmbH says its TransPEG transient pegylation technology can be broadly applied while preserving the pharmacology of the original protein.

Pegylation, which is the covalent attachment of polyethylene glycol (PEG) to another molecule, isn’t applicable to all therapeutic proteins. “It’s clearly size dependent — the smaller the peptide or protein, the more problematic pegylation is,” said CEO Dirk Vetter. “With larger proteins, you have perhaps a 50% chance of being successful.”

Pegylating a molecule at the wrong point can cause it to lose all its therapeutic activity, he said. But in some cases, “even if you pegylate it at the right point, you still see that it gets cleared from circulation by receptor-mediated uptake and related clearance mechanisms. Receptor-mediated clearance of pegylated molecules can be the rate-limiting factor and can prevent prolonging the half-life of a molecule beyond two to three days.”

The company’s solution is a linker chemistry that uses pegylation to make a PEG nanocontainer that encapsulates the protein, thus intentionally inactivating it. The linker chemistry can control the rate at which a PEG chain falls off the protein, releasing it in its active form.

Once released, the protein has its original pharmacology, Vetter said, “so we don’t need to worry about where we pegylate. For those compounds where pegylation doesn’t work, I think our technology comes in quite nicely.”

The linker is a small molecule with a low molecular weight that has self-cleaving properties. “It’s based on neighbor group effects, where one part of the linker folds around, and it cleaves itself once it is in the bloodstream,” Vetter said. “It’s important that no enzymes are required to catalyze this process, because enzyme levels can vary between patients. In our case, the linker is purposely made not to be a substrate for enzymes.”

Complex has several families of linkers, which can produce a range of half-lives from “12 hours to 100 days,” according to Vetter.

Complex Biosystems GmbH

Heidelberg, Germany
Technology: TransPEG transient pegylation for delivery of small protein and peptide therapeutics
Disease focus: Diabetes and obesity
Clinical status: Preclinical
Founded: 2003 by Harald Rau and Dirk Vetter
University collaborators: University of Heidelberg and University of Marburg
Corporate partners: Not disclosed
Number of employees: 7
Funds raised: €3.2 million ($4.4 million)
Investors: TechnoStart Ventures and Technologie-Beteiligungs-Gesellschaft der Deutschen Ausgleichsbank (tbg/KFW)
CEO: Dirk Vetter
Patents: None issued

PEG has a half-life that is suitable for once-weekly delivery. If the company wants to formulate proteins with half-lives longer than one week, then it will likely use the same linker strategy with a different carrier molecule, like albumin, Vetter said.

Since Complex’s linker self-cleaves under typical homeostatic conditions in human blood, it can be stored and shipped as a lyophilized product or refrigerated in a solution with a low pH. “Lowering the pH and temperature changes the cleavage half-life from about 144 hours to about 100 years,” Vetter said.

Initially, the company will focus on developing peptides and small proteins for which it’s been challenging to achieve a good therapeutic index without pegylation. “There’s a huge opportunity,” Vetter said.

As proof of principle, the company has developed once-weekly injectable formulations of insulin and a GLP-1 analog. Both are in early preclinical development.

Complex (Heidelberg, Germany) has no plan to focus on specific indications, according to Vetter. “At the moment, there are too many opportunities,” he said. “We see our role in moving our programs into clinical trials as quickly as possible. The company plans to move its programs to the end of Phase II prior to partnering them.

The company also partners the TransPEG platform, he added, though the identities of Complex’s partners are not disclosed.

Vetter said that in the medium term, Complex hopes to back-integrate into discovery: “The next step will be to build a proprietary peptide line with our own molecules.”

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## Politics & Policy

### Amending FDARA

Senator Bernie Sanders (I-Vt.) cast the sole dissenting vote in last week’s 93-1 Senate endorsement of the FDA Revitalization Act (S. 1082). The bill reauthorizes PDUFA, medical device user fees and incentives for conducting FDA-requested pediatric trials. Its drug safety provisions have been substantially modified since they were first proposed in 2006, the focus has shifted from pre-approval precautionary measures to bolstering FDA’s ability to detect and act on safety signals from post-approval experience. S. 1082 also does not include a mandate to create a pathway for follow-on biologics. But the final outcome is yet to be decided, as the House of Representatives has yet to begin piecing together its legislative package. The House is likely to attach different drug safety and other provisions to PDUFA reauthorization. Reconciliation of the House and Senate versions will determine the final form of the legislation. Below is a summary of selected changes the Senate ultimately incorporated either as amendments or as modifications to the underlying bill. (A) Agreed on by Senate prior to last week.

<table>
<thead>
<tr>
<th>Amendment no.</th>
<th>Sponsor</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>985</td>
<td>(Sam Brownback, R-Kan.)</td>
<td>Would establish a priority drug review process to encourage development of treatments for tropical diseases; would award a priority review voucher to any company that brings a neglected tropical disease treatment to market. The voucher would be transferable and could be applied to any drug in a company’s pipeline.</td>
</tr>
<tr>
<td>990</td>
<td>(Byron Dorgan, D-N.D.)</td>
<td>Would allow individuals to import prescription drugs freely from Canada; would allow pharmacists to import from a number of industrialized countries. Excludes biologics. The Senate also passed Amendment 1010 (below), which would nullify Amendment 990 for at least the remainder of the Bush administration.</td>
</tr>
<tr>
<td>998</td>
<td>(Chuck Grassley, R-Iowa)</td>
<td>A drug sponsor that failed to comply with any required risk evaluation and mitigation strategy (REMS) could be fined $250,000 for the first 30-day period of noncompliance, a figure that would double for every 30-day period thereafter, not to exceed $2M.</td>
</tr>
<tr>
<td>1004</td>
<td>(Mary Landrieu, D-La.)</td>
<td>Would require FDA to permit the sale of baby turtles as pets so long as the seller used proven methods to effectively treat salmonella.</td>
</tr>
<tr>
<td>1006</td>
<td>(Lisa Murkowski, R-Alaska)</td>
<td>Would modify provisions relating to required experience or certification for prescribing or dispensing certain drugs, and for other purposes, to ensure that distribution restrictions did not prevent residents of remote areas from receiving therapy.</td>
</tr>
<tr>
<td>1009</td>
<td>(Orrin Hatch, R-Utah)</td>
<td>Would apply Hatch-Waxman exclusivity and patent term restoration to antibiotics; would require FDA to establish and periodically update in vitro standards for determining antimicrobial efficacy; would apply Hatch-Waxman provisions to single enantiomers.</td>
</tr>
<tr>
<td>1010</td>
<td>(Thad Cochran, R-Miss.)</td>
<td>Would make any importation language in S. 1082 contingent on the HHS Secretary certifying that importation would (1) pose no additional risk to the public’s health and safety; and (2) result in a significant reduction in the cost of covered products to the American consumer.</td>
</tr>
<tr>
<td>1011</td>
<td>(Debbie Stabenow, D-Mich.)</td>
<td>Intended to prevent abuse of Citizen Petitions to delay entry of generic drugs by allowing FDA to review and approve an application before it responds to all pending citizen petitions.</td>
</tr>
<tr>
<td>1018</td>
<td>(Jim DeMint, R-S.C.) (A)</td>
<td>Would require FDA to assess the risk evaluation and mitigation strategy (REMS) for the abortion drug Mifeprex (RU-486) within 7 months of the effective date of S. 1082.</td>
</tr>
<tr>
<td>1019</td>
<td>(Robert Casey, D-Penn.)</td>
<td>Expressing “sense of the Senate” that the FDA should enter into a contract with the Institute of Medicine (IOM) to conduct a study concerning measures that may be taken to improve the likelihood that FDA-approved drugs that are safe and effective in treating children with orphan diseases are made available and affordable for pediatric indications.</td>
</tr>
<tr>
<td>1025</td>
<td>(Charles Schumer, D-N.Y.) (A)</td>
<td>Expressing the “sense of the Senate” that legislation should be enacted giving FDA authority and flexibility to approve follow-on biologics via an abbreviated approval pathway; could be replaced with specific legislation if consensus is reached prior to reconciliation of House and Senate versions of FDARA.</td>
</tr>
<tr>
<td>1041</td>
<td>(Barack Obama, D-Ill.)</td>
<td>Would require an Institute of Medicine (IOM) report that includes recommendations to improve federal oversight and regulation of genetic tests.</td>
</tr>
<tr>
<td>1047</td>
<td>(Pat Roberts, R-Kan.)</td>
<td>Would provide for voluntary pre-review submission of DTC ads to FDA; replaces language that would have given FDA authority to impose a 2-year post-approval moratorium on DTC with the power to impose civil monetary penalties for ads that are false or misleading; $150,000 for a first offense and $300,000 for additional offenses.</td>
</tr>
</tbody>
</table>
Ebb & Flow

Striking while the iron is hot

By Stacy Lawrence
Senior Writer

A few cancer vaccine companies and insiders managed to capitalize on rising share prices during the brief window between the March 29 FDA panel vote in favor of Dendreon’s Provenge sipuleucel-T for prostate cancer and the double dose of bad news last week: an approvable letter from FDA for Provenge and an FDA panel vote against approval of IDM Pharma’s Junovan mifamurtide (see “The Thrill is Gone?”).

Cell Genesys, which has a Phase III prostate cancer vaccine, raised $60 million on April 11 in a registered direct offering of 10.8 million units at $5.55. Each unit consists of a share and a five-year warrant to purchase 0.2 shares, with each whole share warrant exercisable at $7.18 per share. Prior to the offering, CEGE was at $6.08 but since has slumped to $4.13 on Friday.

Genitope (GTOP) also raised $21 million in an April follow-on of 5.5 million shares at $3.85. Prior to proposing that financing, GTOP was at $4.54. The stock now is back to $3.58. GTOP’s MyVax vaccine is in Phase III testing for follicular non-Hodgkin’s lymphoma (NHL), with data expected by year end.

In the penny stock space, Avax (AVXT) raised $10 million in April through the sale of 80 million shares at $0.13, with 5-year warrants to purchase an additional 80 million shares. The stock has deteriorated to $0.27 from a high of $0.40 immediately following the Provenge panel.

The company’s melanoma vaccine is in a Phase III trial. Among cancer vaccine company executives and board members, only those at DNDN made a quick move to cash in. President and CEO Mitchell Gold sold shares at $13.46 on April 2, bringing in $2.7 million (see BioCentury, April 9).

Director Ruth Kunath also sold almost $1.2 million of DNDN shares at $14.83 to $24.35 over several days in early April. Director Bogdan Dziurzynski sold at $15.04 a share, bringing in $376,000.

Following last week’s approvable letter, DNDN was off $13.28 (68%) to $6.11. IDM (IDI) also fell $6.35 (71%) to $2.59 on the week, after FDA’s Oncologic Drugs Advisory Committee recommended against approval of Junovan to treat newly diagnosed high-grade osteosarcoma. The company expects an FDA decision in late August (see “A Roll of the Dice,” A19).

As goes DNDN . . .

A few non-vaccine companies with late-stage prostate cancer treatments also slipped on DNDN’s approvable letter for Provenge. GPC Biotech (FSE:GPC; GPCB) was off €0.18 to €21.12, while GPCB was down $0.88 to $28.25 on NASDAQ. The company is anticipating an FDA decision in August for satraplatin for use in combination with prednisone to treat patients with hormone-refractory prostate cancer (HRPC) after chemotherapy has failed.

GPC has exclusive rights to the oral platinum compound from Spectrum (SPPI), which was down $0.10 to $6.45 on the week.

Last year, GPC granted European marketing rights for satraplatin to Pharmion (PHRM), which expects to submit an MAA this quarter. PHRM fell $1.15 to $30 last week, when it also raised $120 million through the sale of 4 million shares at $30 in a follow-on underwritten by Banc of America Securities; Cowen; Pacific Growth; Friedman, Billings, Ramsey; and HSBC. When PHRM proposed the offering last week, its share price was $30.99.

GTx (GTXI), whose Acapodene toremifine is in Phase III trials, was off $1.37 to $18.61 on the week. Phase III data for the non-steroideal selective estrogen receptor modulator (SERM) are due in the fourth quarter.

Novacea (NOVC), which has Asentar in a Phase III trial to treat advanced prostate cancer, eroded $0.69 to $8.17. The candidate is a high-dose, oral formulation of calciotriol hormone, a biologically active form of vitamin D.

$70M runway

Cardiovascular company Portola last week chalked up the second largest venture round this year, garnering $70 million to get its lead drug to Phase II and Phase III clinical results for three candidates. The funding trails only the $175 million that went to specialty pharma EUSA for the acquisition of oncology company OPI in March and matches the funding for infectious disease company Targanta in February (see “Targeting an IPO,” A20).

The series C round included new investors Brookside Capital; AllianceBernstein; Teachers Private Capital; Goldman Sachs; T. Rowe Price; IBT Management; and CIDC Consultants, which joined existing investors Abingworth Management; Alta Partners; Advanced Technology Ventures; Frazier Healthcare Ventures; MPM Capital; Prospect Venture Partners; and Sutter Hill Ventures.

Originally spun out of the Cor Therapeutics subsidiary of
Ebb & Flow, from previous page

Millennium (MLNM) in 2003, Portola has raised $137 million in venture capital and an additional $20 million in debt financing from Hercules Technology Growth Capital.

Portola’s lead candidate, PRT054021, has completed a Phase II trial to prevent venous thromboembolism after orthopedic surgery. The company hopes to move the oral Factor Xa inhibitor into Phase III testing for the indication in early 2008.

Portola also has IV and oral formulations of ADP receptor antagonist PRT060128 to block platelet aggregation, which is expected to enter Phase II trials in 2H07.

Alta’s Farah Champsi, who sits on Portola’s board, told Ebb & Flow: “The plan is to take the company public some time in 2008 and to continue clinical development. Then hopefully we will partner one of the programs and see where we are in terms of a potential exit opportunity.”

She added: “They are in an area that is strategically important to filling the pipelines of several large pharmaceutical companies.” “This is a company that is pursuing major categories,” said MPM’s Ashley Dombkowski. “They aren’t niche; they aren’t specialty pharma.”

Quick uptick

Endocrine disorder company Biodel (BIOD) priced its IPO at $15 — the middle of the proposed range — and surged $3 (20%) to $18 on its first day of trading Friday. The positive reception has been the norm for biotech IPOs this quarter, as four of five offerings on U.S. exchanges have traded up.

BIOD sold 5 million shares, raising $75 million and valuing the company at $291 million. The company’s VIAject injectable recombinant human insulin is in two Phase III trials for Type I and II diabetes. BIOD expects to complete the trials and submit an NDA under the 505(b)(2) regulatory pathway in 2008. The company also hopes to have Phase II data in 2008 for VIAtab, its oral sublingual prandial insulin.

On the road show, CFO F. Scott Reding said the company is capital efficient, having previously raised only $27 million. BIOD took VIAject from IND through Phase II on only $5 million and expects to spend only $15 million on Phase III testing.

Reding pegged the company’s monthly burn at $2 million for the remainder of the year. After completing Phase III and submitting an NDA next year, he said BIOD expects to enter a partnership.

“We want to wait until we have Phase III data in hand,” he said. BIOD hopes to retain co-commercialization rights in specialized markets like juvenile diabetes.

Underwriters were Morgan Stanley; Banc of America; Leerink; and Natexis Bleichroeder.

Targeting an IPO

Investors in Targanta’s $70 million series C round in February may not have long to wait for an exit, as the infectious disease company last week filed to raise up to $86 million in an IPO through underwriters Credit Suisse; Cowen; Lazard; and Leerink Swann.

Targanta focuses on antibiotics to treat hospital-acquired infections. It expects to submit an NDA for oritavancin to treat complicated skin and skin structure infections (cSSSIs) in IQ08 and is hoping for FDA approval in late 2008.

The intravenous antibiotic was acquired in 2005 from Intermune (ITMN), which itself had acquired oritavancin from Eli Lilly (LLY).

Targanta’s principal stockholders include Brookside Capital (15.2% prior to the IPO); ITMN (15.2%); Skyline Ventures (13.2%); VenGrowth (11.8%); OrbiMed (11.1%); T2 C2 (7.3%); Canadian Medical Discoveries (7.1%); Seaflower Ventures (7%); and Radius Ventures (6.1%).

The company has raised $85 million in venture capital since it was founded in 1997, with an additional $33 million in debt financing. At Dec. 31, prior to the latest venture infusion, Targanta had $12.5 million in cash. In 2006, its net loss was $29 million.

IPO watch

Addex and Helicos provided additional details about their proposed IPOs last week, while ImaRx refilled after pulling its proposal in December. Hormone therapy company EndoCeutics also lowered its range.

Addex, the Swiss neurology and gastrointestinal company, said plans to raise CHF135 million ($111 million) in an IPO on SWX. The company set a range of CHF58-CHF75 and expects to offer 1.8-2.3 million shares. At the middle of that range Addex would be valued at CHF400 million ($330 million).

Bookbuilding is slated through May 21, with the issue expected to price and start to trade on May 22. The IPO will consist of a public offering in Switzerland and private placements to institutional investors elsewhere.

In April, Addex reported positive Phase IIb data for ADX10059 to treat gastroesophageal reflux disease (GERD) and migraine. Phase IIb trials are expected to start in the first quarter of 2008 (see BioCentury, April 23).

The negative allosteric modulator of metabotropic glutamate receptor subtype 5 (mGluR5) is also in Phase IIa trials to treat acute anxiety.

The company had CHF34.2 million ($28.2 million) in cash at March 31. Lehman Brothers was lead manager, with Credit Suisse, UBS Warburg and Bank of America as co-managers.

See next page
Scaling back

ImaRx has refiled its IPO after pulling it last year based on market conditions. This time, the vascular disorder company is looking to sell 3 million shares at $6.50-$7.50 in an offering underwritten by Maxim Group. At $7, the deal would raise $21 million and value ImaRx at $63.4 million.

That’s a big step down from the company’s original ambitions. ImaRx had been seeking to sell 5 million shares through CIBC World Markets; Jefferies; and First Albany, which would have raised $55 million and valued the company at $195 million at the middle of the proposed $10-$12 range.

Since the end of 2006, ImaRx returned to Abbott (ABT) two Phase III recombinant urokinase programs that it had acquired from the pharma company in April 2006. The biotech continues to market Abbokinase, a tissue culture urokinase to treat acute massive pulmonary embolism that it got from ABT in the same deal.

ImaRx also has SonoLysis therapy in a Phase II/II trial in combination with tissue plasminogen activator (tPA) to treat ischemic stroke. SonoLysis consists of MRX-801 lipid microbubbles that are intravenously administered and locally activated by ultrasound to break up blood clots.

The company had $1.2 million in product sales, grants and other revenue in IQQ7, with an operating loss of $2.2 million. At March 31, ImaRx had $2.8 million in cash.

Meanwhile, Canadian hormone therapy company EndoCeutics lowered its range to $7-$9 from $11-$13. The company still plans to sell 5.75 million shares in the NASDAQ deal, which is being underwritten by First Albany; Oppenheimer; and Stifel, Nicolaus.

At $8, EndoCeutics would raise $46 million and be valued at $146 million. The company originally filed in February to raise up to $75 million.

In 2H07, EndoCeutics plans to start a Phase III trial of lead candidate acobifene, a selective estrogen receptor modulator (SERM), to treat advanced breast cancer in women who have failed hormone therapy.

VC’s cancer focus

Switzerland’s Nextech Venture is raising a new fund dedicated to developing companies focused on cancer therapeutics. The fund has initially closed on €25 million ($34 million), Founding Partner and CEO Alfred Scheidegger told Ebb & Flow.

Nextech will fund companies with at least proof of concept in animals and support them through Phase II data. The new fund already has made its first investment: German cancer company Ganymed, which has a preclinical lead compound slated to start Phase I/IIa testing for gastric cancer next year (see BioCentury, April 23).

“The came up with this business model, we thought that we can’t be experts in all other fields and we can’t have the same quality network of experts in other fields,” Scheidegger said.

Nextech manages three life sciences funds, representing a total of CHF110 million ($91 million).

Fund watch

Emergent Technologies closed its fourth fund, dedicated to commercializing biotechnology derived from research within the University of Texas institutions. The $27.1 million fund will be distributed among up to 30 different technology applications.

LPs include several large and institutional investors. About 70% of the investors are based in San Antonio, with the remainder coming from around Texas.

The fund has invested in two companies formed in the last six months: drug delivery company Mimetic Solutions and chemiluminescent diagnostics company Beacon Sciences. Emergent plans to launch several other companies this year.

Venture tracks

Bill Ringo has joined Sofinnova Ventures as an executive-in-residence. He had been president and CEO of Abgenix and is on the boards of ophthalmic and respiratory company Inspire (ISPH), cancer therapeutic company Allos (ALTH) and cardiovascular company Portola.

Vivo Ventures promoted Chen Yu to partner from principal. The firm has more than $650 million under management.

Banker tracks

Jean-Yves Coste joined the Cowen Group as director of its European life sciences business. Previously, he was the head of M&A for Boehringer Ingelheim.

Analyst tracks

Zhining Xu joined Seymour Pierce as a life sciences analyst; Xu came from Barclays Capital.

Accounting tracks

Glen Giovannetti has been promoted to leader of Ernst & Young’s new Global Biotechnology Center in Boston. He had been the business risk services leader for the Pacific Northwest. Scott Sarazen also was appointed as the global markets leader within the center; he was SVP for life sciences with MassDevelopment.

Regulatory milestones

Amgen (AMGN) lost $7.44 (12%) to $56.30 on the week, while Johnson & Johnson (JNJ) lost $2.21 to $62.27 after FDA’s Oncologic Drugs Advisory Committee recommended in a 15-2 vote that FDA narrow the chemotherapeutic-induced anemia indication for Aranesp darbepoetin alfalfa and Epogen epoetin alpha from AMGN and Procrit epoetin alpha from JNJ. The drugs also are approved to treat anemia in patients with chronic kidney disease (see Cover Story).

Dor (DORB) lost $0.48 (69%) to $0.22 on the week after FDA’s Oncologic Drugs Advisory Committee recommended against approval of orBec beclomethasone to treat gastrointestinal graft-versus-host disease (GVH). The NDA for the corticosteroid has a July 21 PDUFA date (see B10).

Schwarz (FSE:SRZ) was off 0.49% to 105.51 on the week after FDA approved an NDA for Neupro rotigotine to treat early stage Parkinson’s disease (PD). The dopamine D2 receptor agonist patch is already approved for the indication in Europe. SRZ is being acquired by UCB Group (Euronext:UCB).

Somaxon (SOMX) was off 2.03% to $15.97 on Wednesday after it said submission of an NDA for Silenor doxepin to treat insomnia might be pushed back to IQQ8 from 3Q07 after FDA requested...
that results from an ongoing 26-week transgenic mouse carcinogenicity study be included in the initial application. The company had planned to submit the data during the NDA review process. Silenor is a low-dose tricyclic doxepin. SOMX was off $2.79 to $15.16 on the week.

Clinical milestones

Inspire (ISPH) was off $0.80 (11%) to $6.68 on the week after its 0.1% dose of epinephrine met the primary endpoint in a Phase II trial to treat or prevent rhinitis. A 0.05% dose of the intranasal antihistamine missed the primary endpoint. ISPH has exclusive North American rights from Boehringer Ingelheim (see B1/2).

Ista (ISTA) lost $0.48 to $6.32 on the week after bepotasine met one of two primary endpoints in a Phase II/III trial to treat allergic conjunctivitis (see B1/3). The company plans to submit an NDA in 2H08. It has exclusive North American rights to the eye drop formulation of the selective histamine H1 receptor antagonist from Senju.

NicOx (Euronext:COX) was off €0.81 to €20.63 on the week, while partner Axcan (TSX:AXP; AXCA) lost C$0.70 to C$18.95 in Canada after deciding to discontinue development of NCX 1000. The decision was based on preliminary data from a Phase Ila trial to treat portal hypertension, which did not show sufficient efficacy (see B12).

The partners had been developing the nitric oxide-donating derivative of ursodeoxycholic acid (UDCA) to treat chronic liver diseases under a 2002 deal. On NASDAQ, AXCA lost $0.78 to $17.02 last week.

Ebb & Flow

Immunomedics (IMMU) was off $0.39 to $4.91 on the week after the autoimmune and cancer company raised $24 million in a registered direct offering.

Peptech (ASX:PTD; LSE:PTDXX) lost A$0.22 to A$1.70 on the week’s news it will acquire fellow antibody company EvoGenix (ASX:EGX) for A$156 million ($128.1 million), or A$1.12 per share in cash and stock. In London, PTDX was down 4.5p to 74.5p. EGX was up A$0.15 to A$1.00 on the week’s news it will acquire fellow antibody company Ebb & Flow, from previous page

London & the Continent

Karo Bio (SSE:KARO) gained SEK0.10 to SEK15.90 on Friday after raising SEK406 million ($60.2 million) in a rights issue through the sale of 38.7 million shares at SEK10.50. The price is a 42% discount to KARO’s close of SEK18 on March 26, the day before the deal was announced. The company’s KB2115, a thyroid hormone receptor agonist, is expected to complete Phase Ila testing for dyslipidemia this half. On the week, the stock was down SEK0.90 to SEK15.90.

Speedel (SWX:SPPN) was off CHF5.50 to CHF16.45 on the week after an article published in the American Journal of Hypertension claimed that Tekturna aliskiren is no more effective than other drugs available to control hypertension due to reactive renin secretion. FDA approved the direct renin inhibitor to treat hypertension in March.

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

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EPS watch

Digene was the big loser last week — down 9% — despite reporting EPS that met the Street consensus and 320% growth over 1Q06. Last week, the U.S. District Court for the State of Delaware denied the diagnostic company’s motion for a preliminary injunction against Ventana Medical Systems (VMSI) in an ongoing patent infringement case covering uses of HPV types 35 and 44 in VMSI’s INFORM HPV Family 16 and Family 6 probe products. (A) Results for fiscal 2Q07; (B) Results for fiscal 3Q07; Mcap in $M

<table>
<thead>
<tr>
<th>Company</th>
<th>1Q07 EPS est</th>
<th>1Q07 EPS actual</th>
<th>Outcome</th>
<th>Growth from 1Q06</th>
<th>5/11 cls</th>
<th>Wk chg % chg</th>
<th>Mcap chg</th>
<th>5/11 Mcap</th>
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<tr>
<td>Axcan (TSE:AXP; AXCA) (A)</td>
<td>$0.24</td>
<td>$0.34</td>
<td>Beat by $0.10</td>
<td>100%</td>
<td>$17.02</td>
<td>-$0.78</td>
<td>-4%</td>
<td>$35.9</td>
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<tr>
<td>Bayer (FSE:BAY; BAY)</td>
<td>NA</td>
<td>€1.26</td>
<td>NA</td>
<td>25%</td>
<td>$67.90</td>
<td>-$2.37</td>
<td>-3%</td>
<td>-$1,811.5</td>
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<td>Charles River (CRL)</td>
<td>$0.61</td>
<td>$0.64</td>
<td>Beat by $0.03</td>
<td>33%</td>
<td>$50.40</td>
<td>$1.90</td>
<td>4%</td>
<td>$127.9</td>
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<td>Digene (DIGE) (B)</td>
<td>$0.21</td>
<td>$0.21</td>
<td>Met</td>
<td>320%</td>
<td>$41.91</td>
<td>-$4.06</td>
<td>-9%</td>
<td>-$99.1</td>
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<tr>
<td>Qiagen (FSE:QIA; QGEN)</td>
<td>$0.13</td>
<td>$0.14</td>
<td>Beat by $0.01</td>
<td>8%</td>
<td>$17.22</td>
<td>-$0.28</td>
<td>-2%</td>
<td>-$43.7</td>
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Sales rose 15% to $291.2M from $254.1M in 1Q06. The research tool supplier reiterated its FY07 non-GAAP EPS guidance of $2.43-$2.53 on sales of $1.16-$1.19B.

The fiscal 3Q07 and 3Q06 EPS figures include stock-based compensation and adjust for a 38% tax rate. Total revenues were $52.5M, up 34% from $39.1M in the same period last year. Revenues were driven by a 41% increase in HPV test revenues, which came in at $48.3M.

The research tool supplier posted sales of $127.9M, up 18% from $108.7M in 1Q06.

Analyst picks & changes

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<th>Opinion</th>
<th>Wk chg</th>
<th>5/11 cls</th>
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<td>Acorda (ACOR)</td>
<td>Lazard</td>
<td>Joel Sendek</td>
<td>Price target</td>
<td>Buy</td>
<td>-5%</td>
<td>$23.97</td>
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<tr>
<td>Advanced Life (ADLS)</td>
<td>Lazard</td>
<td>Matthew Osborne</td>
<td>Price target</td>
<td>Buy</td>
<td>-12%</td>
<td>$3.06</td>
</tr>
<tr>
<td>Aeterna Zentaris (TSX:AEZ; AEZS)</td>
<td>Dundee</td>
<td>David Martin</td>
<td>Rating change</td>
<td>Under review (from market outperform)</td>
<td>-11%</td>
<td>$3.54</td>
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<td>Amgen (AMGN)</td>
<td>Bane of America William Sargent Securities Jefferies</td>
<td>Adam Walsh</td>
<td>Price target</td>
<td>Buy</td>
<td>-12%</td>
<td>$56.30</td>
</tr>
<tr>
<td></td>
<td>Lazard</td>
<td>Joel Sendek</td>
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<td>Sell (from buy)</td>
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<td></td>
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</tr>
</tbody>
</table>

Martin’s rating change came after Solvay (Euronext:SOLB) returned its remaining rights to AEZ’s cetorelix (see B2). Last year, SOLB returned its rights to the GnRH/LHRH receptor antagonist to treat benign prostatic hyperplasia (BPH) but kept rights to treat endometriosis (see BioCentury, Feb. 6, 2006).

Amgen lowered its target to $64 from $72 after FDA’s Oncologic Drugs Advisory Committee voted in favor of FDA placing more restrictions on erythropoiesis-stimulating agents (ESAs) Aranesp and Epogen from AMGN and Procrit from Johnson & Johnson (JNJ) in cancer patients (see Cover Story).

Walsh lowered his target to $55 from $64 on the ESA news.

Spendek lowered his target to $50 from $70 on the ESA news.

Axcan (TSE:AXP; AXCA) | Dundee | David Martin | Price target | Neutral | -4% | $17.02 |

Martin raised his target to $19 from $18 and increased his FY07 EPS estimate to $1.22 from $1.11 after AXP reported strong fiscal 2Q07 results (see “EPS Watch”).

See next page
Analyst Picks & Changes, from previous page

<table>
<thead>
<tr>
<th>Company</th>
<th>Bank</th>
<th>Analyst</th>
<th>Coverage</th>
<th>Opinion</th>
<th>Wk chg</th>
<th>$/11 cls</th>
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<td><strong>Dendreon (DNDN)</strong></td>
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<td>Charles Duncan</td>
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<td></td>
<td>Needham</td>
<td>Mark Monane</td>
<td>Downgrade</td>
<td>Hold (from buy)</td>
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</table>

Duncan lowered his target to $13 from $26 after DNDN received an FDA approvable letter for Provenge sipuleucel-T to treat asymptomatic patients with metastatic, androgen-independent prostate cancer (see “A Roll of the Dice,” A10). However, he remains optimistic an interim analysis of DNDN’s Phase III IMPACT trial will lead to Provenge’s approval.

Monane cited uncertainty about the development path for Provenge and a lack of significant news flow in the next 12-18 months.

| **Flamel (FLML)** | Merriman Carhan Ford | E. Russell McAllister | Other | Buy | 5% | $28.72 |

McAllister lowered his FY07 and FY08 EPS estimates to $0.27 from $0.88 and to $2.13 from $2.20, in part due to a late launch “relative to expectations” for Coreg CR carvedilol to treat hypertension, heart attack and heart failure (see BioCentury, March 26). He also lowered his FY07 and FY08 revenue estimates to $84.3M from $105.6M and to $160.2M from $163.1M. GlaxoSmithKline (LSE:GSK; GS) markets the once-daily, extended-release formulation of the adrenergic receptor beta blocker, which uses FLML’s Micropump technology.

| **InterMune (ITMN)** | JMP Securities | Adam Cutler | Price target | Market outperform | -8% | $25.50 |

Cutler raised his price target to $39 from $34 to reflect faster than expected enrollment in the Phase III CAPACITY trials of pifithrin, an oral p38 MAP kinase inhibitor, to treat idiopathic pulmonary fibrosis (IPF) (see BioCentury, March 26). He now expects pifithrin revenues starting in 2009 rather than 2010.

| **Isis (ISIS)** | Fortis | Geraldine O’Keefe | Price target | Buy | -1% | $9.88 |

O’Keefe raised her target to $18 from $13 after ISIS partnered with Bristol-Myers (BMY) to discover, develop and commercialize antisense compounds targeting PCSK9 (see “Silencing a Silent Killer,” A14).

| **Ista (ISTA)** | Jefferies | David Windley | Price target | Hold | -7% | $6.32 |
| Lazard         | Megan Murphy | Downgrade | Hold (from buy) |       |       |
| Punk           | Geoffrey O’Brien | Price target | Buy |       |       |

Windley lowered his target to $6 from $10 after ISTA got an FDA not approvable letter for T-Pred, a fixed combination of 0.3% tobramycin and 1% prednisolone, to treat steroid-responsive inflammatory ocular conditions where risk of bacterial infection exists (see B10).

Murphy removed T-Pred from her forecast.

O’Brien raised his target to $12 from $11 after ISTA reported positive preliminary Phase II/III data for bepotastine to treat allergic conjunctivitis (see B13). He also expects Phase IIb data for ISTA’s cabetol sodium to treat dry eye this quarter.

| **Neurochem (TSX:NRM; NRNX)** | Jefferies | Eun Yang | Price target | Hold | -27% | $7.06 |

Yang lowered her target to US$10 from US$13. She believes upcoming Phase III data for Alzhemed trampiosate to treat Alzheimer’s disease (AD) are “highly unpredictable.” The data are expected this quarter.

| **Poniard (PARD)** | Lazard | Matthew Osborne | New | Buy | 2% | $6.95 |

Osborne set an $11 target. He expects safety data from a Phase I trial of picoplatin in colorectal cancer to be presented in June at ASCO, and believes the company already has sufficient data for picoplatin in small cell lung cancer (SCLC) for marketing approval.

| **United Therapeutics (UTHR)** | C.E. Unterberg, Andrew Fein | Upgrade | Buy | 9% | $64.87 |
| Towbin | (from market perform) | | | | |

Fein set an $80 target. He expects positive data from the Phase II TRIUMPH trial of inhaled Remodulin to treat pulmonary arterial hypertension (PAH) in 4Q07.

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‘It’s the BioCentury’™
Queen moves in PDL chess game

By Stacy Lawrence
Senior Writer

Cary Queen, the co-founder of PDL Biopharma Inc., has stepped into the debate over corporate strategy at PDLI, aligning himself with hedge fund Third Point’s campaign to oust CEO Mark McDade.

Queen was with PDLI for 15 years, primarily as head of its research department and then as a director. In February 2006 he became a consultant to the antibody company.

Last week, Queen posted an open letter to a web site and released it on a wire service. His letter to the company’s board called for “a new direction at PDL that emphasizes efficiency, focus on product development, and profitability, under the leadership of a new Chief Executive Officer.”

In this view, Queen told Ebb & Flow, things began to go wrong “almost from the beginning and certainly within the first year” of McDade’s tenure as CEO, which began about four and a half years ago. “There was a significant exodus of skilled personnel from the company because he was attempting to industrialize the company’s research department, which was quite science-based,” said Queen.

But the rap on PDLI — and the reason McDade was recruited — was that the company had only one product, Zenapax, to show for 16 years of work, and that the company had been run more as a science project than a commercial enterprise. Early on in his tenure, McDade had said he wanted to add biology and immunology to validate compounds, establish minimum performance for its antibodies and narrow the focus to areas where the company could be competitive. PDLI also was short on targets (see BioCentury, Aug. 29, 2005, Feb. 10, 2003 & Oct. 6, 2003).

In last week’s letter, Queen wrote that PDLI’s purchase of ESP Pharma Inc. for $486.6 million in cash and stock in 2005 was “ill-considered,” because the specialty pharma company had “two niche non-antibody cardiovascular drugs” that had “absolutely nothing to do with PDL’s business of developing novel antibodies” in cancer and autoimmune diseases.

As a member of the board, Queen said in the letter, he protested the acquisition and said he believes that the significant royalty stream from the patents related to the humanization of antibodies would have been enough to support R&D while keeping PDLI focused on developing its pipeline.

In 2006, royalties, licensing and collaboration accounted for 60% of PDLI’s $414 million in revenue, with the remaining 40% coming from product sales.

Queen’s letter also complained that the clinical development of Nuvion visilizumab was delayed by two years because the research focus was diverted to the acquired products. Nuvion is slated to start Phase III trials to treat inflammatory bowel disease (IBD) mid-year.

Queen blamed the lack of investor confidence in PDLI on McDade’s decision in May 2006 to cut PDLI’s non-GAAP net income guidance by 60-80% in anticipation of funding a Phase III trial to demonstrate the safety of one of the acquired candidates, ularitide, which then was canceled.

He also charged that McDade’s tenure had been marked by “unchecked” spending, with headcount almost tripling and R&D spending more than tripling. Queen is particularly peeved by an “expensive” build-out of new headquarters.

PDLI has several years before its antibody humanization patents expire in 2014, while its main revenue-generating product, the intravenous hypertension treatment Cardene, goes off patent in 2009 or 2010, said Queen. He hopes to see the company refocus on its development pipeline and control spending under new management.

“One wishes to see one’s life’s work in good hands and unfortunately I don’t feel it is right now,” Queen told BioCentury.

In a letter to shareholders to be sent this week, which PDLI provided to BioCentury, the company acknowledges that “2006 had its challenges, as we experienced what most drug development companies face on their path to success: unpredictable clinical developments.”

These include the “Phase III failure of terlipressin, a delay in the Nuvion clinical program due to challenges in clinical site setup, a necessary strategic decision regarding ularitide and the discontinuation of our daclizumab co-development partnership with Roche” (see BioCentury, Jan. 22).

Nevertheless, PDLI said, it has advanced its pipeline through positive results for “daclizumab in multiple sclerosis (MS) and volociximab in several solid tumor studies, while moving a new antibody into Phase I human study for refractory multiple myeloma.”

The company also said it is taking steps “to improve our efficiency, refine our processes and improve outputs from our pipeline.” These include the addition of new CMO Mark McCamish, formerly CMO and VP of clinical development at Perlegen Sciences Inc., in early 2007.

As to the headquarters issue, PDLI CFO Andrew Guggenhime said on a May 2 conference call that “the leases on the three buildings that we rent in Fremont expire between the end of this year and March 2008.” He added that the new site in Redwood City was determined to be the “most cost effective option” after a two-year search by outside advisors.

Third Point has been calling for McDade to leave since March, and wants the company broken into two entities, one focused on product sales and the other on R&D (see BioCentury, April 16).

According to SEC filings, the firm held no stake in PDLI at March 31, 2006. The hedge fund gradually acquired holdings first reported at the end of 2Q06 at 150,000 shares. As of April 18, Third Point reported it held 11.2 million shares, or 9.7% of PDLI.

Queen holds the largest insider stake in PDLI, at almost 2 million shares. He has neither sold shares nor exercised options since December 2005.

In January, McDade sold more than 68,000 shares for $1.4 million. He still holds 62,000 shares.

PDLI finished the week up $0.40 to $26.03.
Playing the China market

By Stacy Lawrence
Senior Writer

Look for more Chinese drug companies to go public on U.S. stock exchanges this year, as many of these companies hope to become aggregators in what is a fragmented market — and they like the idea of using U.S. shares as currency.

Tech companies, like search engine play Baidu.com (BIDU), have primed the pump for Chinese companies on U.S. markets. But tech company stories and their often U.S.-educated management have been much more accessible to investors than healthcare, noted David Parrot of Piper Jaffray, an underwriter on last month’s IPO for Chinese generic company Simcere Pharmaceutical Group (SCR, Nanjing, China) (see BioCentury, April 23).

Still, U.S. investors have become interested in China’s enormous healthcare market. They have been trying to understand “how do you play that?” Parrot said.

Parrot also pointed to positive experiences with American Oriental Bioengineering Inc. (AOB, Shenzhen, China), a traditional Chinese medicine company that began trading onNYSE last December via a reverse merger. AOB climbed from an opening share price of $1.75 to a peak of $14.19 early in the first quarter. Last week, AOB closed at $11.04, giving it a market cap of $713.3 million.

“That’s been a wildly successful stock. The reason AOB has taken off is because they have consolidated a number of companies and delivered several quarters of incredible growth,” Parrot told BioCentury. “Liquidity has come after that.”

Parrot noted AOB has been primarily a retail play that has just started to attract institutions. Morgan Stanley is the single largest institutional holder, with more than 3% of outstanding shares at Dec 31. Among top mutual fund holders have been Federated Kauffman Small Cap Fund and Forward Funds Small Cap Equity Fund. Each held almost 1% stakes as of Jan 31 and Feb. 28, respectively.

Indeed, the reception to the Chinese stories has been mixed. SCR, a generics company, also has seen some uplift. It closed last week at $16.65, up $2.15 from its IPO price of $14.50 and boosting its market cap to just over $1 billion.

SCR joined traditional Chinese medicines company Tongjitang Chinese Medicines Co. (TCM, Shenzhen, China) on the NYSE, while biotech 3SBIO Inc. (SSRX, Shenyang, China) debuted onNASDAQ. All three companies have significant revenue and are profitable. All three also have research pipelines.

SSRX raised $115 million and, at $16 a share, had a post-money valuation of $344 million in February, while TCM garnered $84 million and at $10 was valued at $334 million in March.

Last week, SSRX closed at $10.20, leaving its market cap at $219 million, but TCM has edged up to $10.30, pushing its valuation to $344 million.

As a traditional Chinese medicine play, TCM may be insulated. Parrot noted that traditional Chinese medicines are protected by the state, which “won’t allow a bunch of copycats” and limits the number of marketed products to two or three.

TCM is likely attractive to investors “who want exposure to China in a pure way, because this is not a company that is going to widely distribute products in the Western world,” said Bill Kridel of Ferghana Partners.

Indeed, COO Justin Chen confirmed that the “majority of the investors were emerging markets/China investors,” with participation from some healthcare funds. The IPO was 4X oversubscribed with more than 100 investors participating.

By contrast, Kridel noted, SSRX’s biosimilars business may be a more difficult sell to U.S. investors because “biogenerics don’t have a clear business pathway.”

SSRX CEO Jing Lou characterized his company’s investors as “a mix of biotech, emerging market and pharmaceutical investors.”

TCM and SCR both hope to follow AOB’s path toward acquisitions. The “traditional Chinese medicine industry is a highly fragmented sector in China, with over 1,200 manufacturers, but average annual sales of less than RMB100 million ($13 million) each,” TCM’s Chen said.

“We expect consolidation in the coming 3-5 years and we consider Tongjitang a consolidator in this sector.”

— TCM’s Justin Chen

“With a clear business pathway.”

“SSRX CEO Jing Lou characterized his company’s investors as “a mix of biotech, emerging market and pharmaceutical investors.”

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“We expect consolidation in the coming 3-5 years and we consider Tongjitang a consolidator in this sector.”

— TCM’s Justin Chen

“We expect consolidation in the coming 3-5 years and we consider Tongjitang a consolidator in this sector. Shares traded on NYSE could be an effective M&A currency, helping us to achieve this consolidation target,” he noted.

In an SEC filing, SCR noted there were more than 4,700 pharmaceutical manufacturers in China at the end of 2004, with none holding more than a 4% share of the market, which the company sees as an “opportunity for consolidation.”

In the meantime, Parrot said there is a backlog of Chinese drug plays waiting to go out on U.S. markets. Foreign companies file an F-1 with the SEC confidentially, so it’s “not until right before you hit the road that you file publicly,” he said.

Parrot anticipates most of these next IPOs will be largely profitable generics and medicinal chemistry plays. He thinks these types of companies, with their cost advantages, could connect with U.S. investors.

So far, Chinese biopharmaceutical plays have mostly attracted U.S. funds invested in other areas in China that are looking to diversify into healthcare, Parrot said. “I haven’t seen any of the traditional biotech players here in the U.S. start to poke their toes in yet,” he said.
Online links this week

**Pediatric studies**
Updated list of label changes implemented by FDA to reflect results from pediatric studies.

**Product documentation**
— Activase: NICE recommendation in favor of Activase alteplase to treat acute ischemic stroke, from Genentech Inc. (DNA) and Boehringer Ingelheim GmbH
— Aralast NP: Product approval information including approval letter and label for Aralast NP, an enzyme replacement therapy for patients with alpha-1-antitrypsin deficiency (A1AD) and evidence of lung emphysema, from Baxter Healthcare Corp. (BAX).
— Arcoxia: Slide presentations from the April 12 meeting of FDA’s Arthritis Advisory Committee review of Arcoxia etoricoxib to treat osteoarthritis (OA), from Merck & Co. Inc. (MRK) (see BioCentury, April 16).
— Flonase: FDA warning letter regarding promotional material that the agency determined overstates superiority and omits material facts regarding Flonase fluticasone to treat the nasal symptoms of rhinitis, from GlaxoSmithKline plc (LSE:GSK; GSK).
— Focetria: CHMP EPAR for Focetria pandemic influenza vaccine from Novartis AG (NVS; SWX:NOVN).

— Junovan: Briefing materials for the May 9 meeting of FDA’s Oncologic Drugs Advisory Committee to review Junovan mifamurtide to treat newly diagnosed high-grade osteosarcoma, from IDM Pharma Inc. (IDMI) (see “A Roll of the Dice,” A10).
— Nasonex: FDA warning letter regarding promotional material that the agency determined makes unsubstantiated efficacy and superiority claims for Nasonex mometasone to treat and prevent rhinitis and to treat nasal polyps, from Schering-Plough Corp. (SGP).
— orBec: Briefing materials for the May 9 meeting of FDA’s Oncologic Drugs Advisory Committee to review orBec beclomethasone dipropionate to treat gastrointestinal graft-versus-host disease (GVHD), from Dor BioPharma Inc. (DORB) (see B10).
— Sebivo: CHMP EPAR for Sebivo telbivudine to treat chronic hepatitis B (HBV) in adults with compensated liver disease and evidence of viral replication, from Idenix Pharmaceuticals Inc. (IDIX) and Novartis AG (NVS; SWX:NOVN).
— Tamiflu: CHMP revised EPAR updating the SPC and package leaflet to include neuropsychiatric disorders, cough and vertigo in patients taking Tamiflu oseltamivir to treat influenza in adults and children, from Roche (SWX:ROG).

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| Somaxon (SOMX) | A21, B11 |
| Spectrum (SPPI) | A19 |
| Speedel (SWX:SPPN) | A22 |
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| Stem Cell Innovations (SCLL) | B6 |
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| Tercica (TRCA) | B18 |
| 3SBIO (SSRX) | A26 |
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| ThromboGenics (Euronext:THR) | B22 |
| Tongtang (TCM) | A26 |
| TorreyPines (TPTX) | B3 |
| Transition (TSX:TTH) | B5 |
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| U.S. Genomics | B8 |
| UCB Group (Euronext:UCB) | A21, B11 |
| United Therap (UTHR) | A11, A24 |
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| ZioPharm (ZIOP) | B20 |
| Zymenex | B21 |

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BioCentury 100 Price & Volume Trend

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

BioCentury London Index

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

TFCG Life Sciences Indexes

Weekly change in combined market capitalization. 12-week period. Tier I = market caps>$1B; Tier II <$1B. Base =100 on Dec. 31, 1998.

Price Gains

Stocks with greatest % price increase in the week ended May 11. (Priced above $2.50; 25,000 minimum share volume)

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<tr>
<th>Company</th>
<th>Ticker</th>
<th>$Close</th>
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Price Declines

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

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<td>NRMX</td>
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Volume Gains

Greatest changes in volume above 25,000 shares.

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<tr>
<th>Company</th>
<th>Ticker</th>
<th>Vol(00)</th>
<th>%Chg</th>
<th>$Close</th>
<th>$Chg</th>
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<tbody>
<tr>
<td>Targacept</td>
<td>TRGT</td>
<td>10007</td>
<td>134%</td>
<td>9.370</td>
<td>-0.110</td>
</tr>
<tr>
<td>Paion</td>
<td>PA8</td>
<td>1088</td>
<td>832%</td>
<td>€8.000</td>
<td>€0.050</td>
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<tr>
<td>Methy1Gene</td>
<td>MYG</td>
<td>8666</td>
<td>756%</td>
<td>C3.590</td>
<td>C0.240</td>
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<tr>
<td>SemBioSys</td>
<td>SBS</td>
<td>2498</td>
<td>690%</td>
<td>C2.990</td>
<td>C0.060</td>
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<tr>
<td>Active Biotech</td>
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<td>7914</td>
<td>675%</td>
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<td>C0.240</td>
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<tr>
<td>Cangene</td>
<td>CNJ</td>
<td>3648</td>
<td>541%</td>
<td>C8.000</td>
<td>C0.060</td>
</tr>
<tr>
<td>bioMerieux</td>
<td>BIM</td>
<td>8049</td>
<td>521%</td>
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<td>-€0.400</td>
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<td>ThromboGenics</td>
<td>THR</td>
<td>8976</td>
<td>485%</td>
<td>€11.19</td>
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<td>Pharming</td>
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<td>57264</td>
<td>458%</td>
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<td>Orexo</td>
<td>ORX</td>
<td>2246</td>
<td>364%</td>
<td>SEK133</td>
<td>SEK5.00</td>
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<td>Innogenetics</td>
<td>INNX</td>
<td>7378</td>
<td>333%</td>
<td>€9.260</td>
<td>€1.060</td>
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<tr>
<td>Gentium³</td>
<td>GENT</td>
<td>3464</td>
<td>312%</td>
<td>17.120</td>
<td>-1.350</td>
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</table>

1 IPO during the week. Price change from IPO price.
2 Includes volume from Toronto Stock Exchange
3 Volume figure is of ADSs (ADS = 1 share)

BioCentury 100 Advance-Decline Trend

<table>
<thead>
<tr>
<th>Week ended</th>
<th>BC100 Price level</th>
<th>BC100 Stocks gaining</th>
<th>Gaining vol (00)</th>
<th>BC100 Stocks declining</th>
<th>Declining vol (00)</th>
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<tr>
<td>Apr 13</td>
<td>1770.67</td>
<td>76</td>
<td>5592551</td>
<td>23</td>
<td>3711563</td>
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<td>1788.64</td>
<td>58</td>
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<tr>
<td>Apr 27</td>
<td>1805.35</td>
<td>47</td>
<td>7592363</td>
<td>52</td>
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<td>May 04</td>
<td>1812.84</td>
<td>41</td>
<td>4974684</td>
<td>57</td>
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<td>26</td>
<td>2286957</td>
<td>74</td>
<td>7806170</td>
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Source: Thomson Financial

BioCentury tracks 601 issues that report prices and volume daily. The BioCentury 100 is a subset used to monitor price and volume trends. TFCG Life Sciences Indexes are compiled by Thomson Financial, provider of market intelligence services to publicly held companies.
See You Next Monday in Glasgow

Bio€quity Europe 2007, next Monday and Tuesday in Scotland, is on track to reach record-setting pre-registration, thanks to:

- An unprecedented concentration of biopharmaceutical companies focused on product development and commercialization
- A compelling programme — “Global Visibility” — focused on the best ways to keep cash flowing to Europe’s biotech space
- The opportunity for “Maximum Financial Networking”
- A continuing commitment of the Regional Hosts and Sponsors to nurturing the investment climate for biotechnology in Europe

All together, the best evidence for Europe’s maturing life science industry will be on display at Bio€quity Europe with a group of Presenting Companies that have raised €4.4 billion ($3.5 billion) since the beginning of 2005.

With this money, this group now has advanced:
- 20 drugs on the market
- 9 compounds under review
- 33 programs in Phase III
- 84 Phase II and Phase II/III trials ongoing
- 64 Phase I and Phase I/II trials started
- 145 programs moving toward the clinic

See the Investor-Validated Presenting Companies

There is still time to join the companies, along with their public and private investors and partners in the investment banking community.

Register Online Through Friday, May 18

You also can obtain hotel information from this site, but delegates should act promptly, as space is limited.
BioBusiness for the week ended May 11

Using BioCentury Part II

BioCentury Part II 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; Cancer; Cardiovascular; Chemistry; Combinatorial biology; Computational chemistry/biology; Dental; Dermatology; Diagnostic; Drug delivery; Endocrine; Epigenetics; Gastrointestinal; Gene/Cell therapy; Generics; Genitourinary; Genomics; Hematology; Hepatic; High throughput screening; Infectious; Inflammation; Metabolic; Microarrays; Microfluidics; Musculoskeletal; Neurology; Nutraceuticals; Ophthalmic; Other; Pharmaceuticals; Pharmacogenetics; Proteomics; Pulmonary; Renal; Supply/Service; Transplant; Veterinary

Deals (Page B2)

Abraxis (ABBI)/Cenomed
Aeterna Zentaris (TSX:AEZ; AEZS)/Solvay (Euronext:SOLB)
Affitech/Roche (SWX:ROG)
Akzo (Euronext:AKZ; AKZOY)/Scheringer (SGP)
Alderon/Magellan Bio
ANI Pharma/Solvay (Euronext:SOLB)
Avesta/Manipal AcuNova
Beckman Coulter (BEC)/Biosite (BSTE)/Inverness (IMA)
BG Medicine/U of Texas
Biolex/Gemab (CSE:GEN)
bioMerieux (Euronext:BIM)/NuGen
Brookwood/Targeted Tech
CalcMedica/TorreyPines (TPTX)/CBR Inst
CellCyte (CCYG; FSE:LK6)/Sigma-Aldrich
(SIAL)
Cellectis (Euronext:ALCLS)/GlaxoSmithKline
(LSE:GSK; GSK)
CellTrend/Epigenomics (FSE:ECX)/Myriad (MYGN)
Cortex (COR)/U of Alberta
CuraMedica/Miral (TSX-V:MIP)
Curis (CRIS)&PG (PG)
CytoGenix (CYGX)/Eurogentec
Entelos (LSE:ENTL)/Jubilant Bio
EvoGenix (ASX:EGX)/Peptech (ASX:PTD; LSE:PTDX)
Evotec (FSE:ETV)/Panacos (PANC)
Gamida-Cell/NovaThera
GeminX/Leo Pharma
Gene Logic (GLGC)/Abbott (ABT)
Intas/Viapro (VPRO)
Inverness (IMA)/Orange Medical
Ixis (ISIS)/Bristol-Myers (BMY)
KineMed/MIT
Molecular Medicine/Sigma-Aldrich (SIAL)
NeuroMedx (TSX-V:NMX)/Transition (TSX:TTH)
Phenex/sanofi-aventis (Euronext:SAN; SNY)
Royalty Pharma/New York U
sanofi-aventis (Euronext:SAN; SNY)/SRI
Stem Cell Innovations (SCLI)/H. Lundbeck
(CSE:LUN)
Viragen (VRA)/Memorial Sloan-Kettering
Sales & Marketing (Page B6)
Angiotech (TSE:ANP; ANPI)/Boston Scientific (BSX)
Axela/BioCheck

Other News (Page B6)

Apotex/Bristol-Myers (BMY)/sanofi-aventis
(Euronext:SAN; SNY)
Atrium (TSX:ATB)
AVI (AVI)/U.S. Dept of Defense
Biofusion (LSE:BFN)/U of Sheffield
Cetus
iCeutica
Medics (MRX)
Purdue Pharma

Management Tracks (Page B7)

Advitech (TSX:AVI)
Aeterna Zentaris (TSX:AEZ; AEZS)
Alltracel (LSE:AP)

Beckman Coulter (BEC)
Cytori (CYTX; FSE:XMRA)/In Vitrogen (IVGN)
Expression Pathology/Oridis
Gen-Probe (GPRO)/Millipore (MIL)
Qiagen (FSE:QIA; QGEN)

Regulatory (Page B9)

Abbott (ABT)
Amgen (AMGN)
Cell Therap (CTICD; NMerc:CTIC)
Cipher (TSX:DND)
Dendreon (DNND)
Dor (DORB)
Fabre/Leo Pharma/Novartis (LSE:GSK; GSK)
Helsinn/MGI (MOGN)
IDM (IDMI)
Ista (ISTA)
J&J (JNJ)
Merck (MRK)/sanofi-aventis (Euronext:SAN; SNY)

See next page
Affitech AS, Oslo, Norway
Roche (SWX:ROG), Basel, Switzerland

Business: Antibodies, Cancer

Affitech will apply its phagemid library, high-throughput screening and antibody engineering technologies to produce human MAb s against an undisclosed cancer target. ROG will fund the research and have rights to develop and commercialize the MAb candidates. Affitech is eligible for milestones and royalties. Further terms were not disclosed.

Akzo Nobel N.V. (Euronext:AKZ; AKZOY), Arnhem, the Netherlands
Schering-Plough Corp. (SGP), Kenilworth, N.J.

Business: Genitourinary, Neurology, Veterinary

The U.S. Federal Trade Commission requested additional undisclosed information from SGP regarding its planned acquisition of AKZ’s Organon BioSciences N.V. pharmaceuticals and animal health subsidiary (see BioCentury, March 19). SGP expects the deal to close by year end.

Alderon Biosciences Inc., Durham, N.C.

Business: Diagnostic

Magellan acquired undisclosed IP from Alderon for developing assays to detect metals, nucleic acids, proteins and small molecules. Magellan markets rapid point-of-care analyzers and automated systems for disease pathology and biomarker identification. Further terms were not disclosed.

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See previous page

BioCryst (BCRX)/Roche (SWX:ROG)
Biogen Idec (BIB)/Vernalis (LSE:VER)
Boehringer Ingelheim
Cell Genesys (CEGE)
CombinatoRx (CRXX)
Corcept (CORT)
Critical Therap (CRTX)
Emergent (EBS)
Gemin X
ImmunoCellular (IMUC)
Inspire (ISPH)
Ipsen (Euronext:IPN)/Tercica (TRCA)
KAI
Marinus
Medicure (TSX:MPH; MCU)
MedImmune (MEDI)/Micromet (MITI)
Merck Serono (SWX:SEO)/Micromet (MITI)
Molecular Insight (MIPI)
Neuren (ASX:NEU)
Omrix (OMRI)
Oramed (ORMP)
Pharmos (PARS)
Sinovac (SVA)
Tapestry (TPPH)
Threshold (THLD)
XenoPort (XNPT)
Ziopharm (ZIOP)
Zymenex

See next page
ANI Pharmaceuticals Inc., Baltimore, Md.

Solvay S.A. (Euronext:SOLB), Brussels, Belgium
Business: Supply/Service
SOLB’s Solvay Pharmaceuticals Inc. unit sold its hormone manufacturing facility in Baudette, Minn., to contract manufacturer ANI. ANI will manufacture and supply Solvay’s hormone products such as Estratest esterified estrogen and methyltestosterone tablets to manage menopausal symptoms. Financial terms were not disclosed.

Avestha Gengraine Technologies Pvt. Ltd., Bangalore, India
Manipal AcuNova Ltd., Bangalore, India
Business: Diagnostic, Supply/Service
The companies partnered to develop diagnostics and perform contract research. For diagnostics, Avestha will use its SNP analysis technology to develop molecular diagnostics for all indications and use systems biology to identify novel biomarkers for predictive diagnostics in metabolic and degenerative diseases. Manipal will be responsible for clinically validating resulting diagnostic products. The companies will jointly own resulting IP.

For contract research, Avestha will be responsible for wet chemistry, and Manipal will run clinical trials. Manipal also will run clinical trials for Avestha’s pipeline of follow-on biologics and active botanicals. Financial terms were not disclosed.

Beckman Coulter Inc. (BEC), Fullerton, Calif.
BioSite Inc. (BSTE), San Diego, Calif.
Inverness Medical Innovations Inc. (IMA), Waltham, Mass.
Business: Diagnostics
IMA raised its offer to acquire the 95% of BSTE that it does not already own from $90 per share in cash to $92.50 per share. Last week, BEC raised its offer to acquire BSTE from $85 per share in cash to $90 per share (see BioCentury, May 7). BSTE said IMA’s new bid is “reasonably likely” to be superior to BEC’s latest offer. BEC’s offer expires on May 15, while IMA’s offer expires May 16. Goldman Sachs is advising BSTE.

BG Medicine Inc., Waltham, Mass.
University of Texas M.D. Anderson Cancer Center, Austin, Texas
Business: Pharmacogenetics
BG will apply its biomarker discovery technology to clinical samples provided by the center to discover biomarkers that predict likely responders to certain breast cancer therapies. Further terms were not disclosed.

Biolex Therapeutics Inc., Pittsboro, N.C.
Genmab A/S (CSE:GEN), Copenhagen, Denmark
Business: Antibodies, Biomanufacturing
GEN will evaluate Biolex’s LEX System for protein expression and antibody optimization as a potential manufacturing platform for antibodies developed with GEN’s UniBody technology. Further terms were not disclosed.

bioMerieux S.A. (Euronext:BIM), Marcy l’Etoile, France
NuGen Technologies Inc., San Carlos, Calif.
Business: Genomics, Supply/Service, Diagnostic
The companies cross-licensed nucleic acid amplification technologies. BIM received non-exclusive rights to NuGen’s amplification technologies to develop and market in vitro diagnostic tests. BIM plans to integrate NuGen’s technologies to develop an automated microarray-based assay to diagnose cancer. NuGen received non-exclusive rights to BIM’s linear amplification technologies using chimeric primers including OEM rights for the research market.
Seperately, NuGen will supply BIM with the WT-Ovation RNA Amplification System for gene expression analysis, which BIM plans to sell with its diagnostic kits. Further terms were not disclosed.

Brookwood Pharmaceuticals Inc., Birmingham, Ala.
Targeted Technology Ventures LLC, San Antonio, Texas
Business: Cardiovascular
Brookwood and Targeted formed a joint venture called Aeon Bioscience Inc. to develop a drug-eluting stent. Brookwood will design and develop a biodegradable polymer and develop a coating process. Targeted will help design and commercialize the stent. Aeon raised an undisclosed amount in a series A round last month. Brookwood President and CEO Arthur Tipton also will be Aeon’s president. Targeted Principal Paul Castella also will be Aeon’s CBO.

CalciMedica Inc., La Jolla, Calif.
TorreyPines Therapeutics Inc. (TPTX), La Jolla, Calif.
CBR Institute for Biomedical Research, Boston, Mass.
Business: Autoimmune, Inflammation
CalciMedica purchased TPTX’s patent application covering uses of

Genetics

FINANCIAL NEWS

Completed Offerings (Page B21)
Allon (TSX:NPC)
AMDL (ADL)
Avestha
Avid Radio
Bioenvision (BVIN)
CombiMatrix (CBMX)
Epigenomics (FSE:ECX)
Immunomedics (IMMU)
Javelin (JAV)
Karo (SSE:KARO)
Kinaxo
MorphoSys (FSE:MOR)
Pharmon (PHRM)
Portola Pharma
Progen (ASX:PGL)
Sidec
StrataGent Life Sci
ThromboGenics (Euronext:THR)
Upstream (UBPS)
Proposed Offerings (Page B22)
4SC (FSE:VSC)
ImaRx
PolyMedix
Targanta
Amended Offerings (Page B22)
Addex
Endoceutics
Helicos
Other Financial News (Page B23)
Conatus
Emergent
Gilead (GILD)
Nextech
Oragenics (ONI)
Pluristem (PLRS)
Shire (LSE:SHP; SHPGY)
‘It’s the BioCentury’™
Deals, from previous page

stromal interaction molecule-1 (STIM-1) for regulating Ca release-activated Ca (CRAC) channels. CalciMedica also obtained NGX53187 and other preclinical compounds that inhibit CRAC channels and block the immune response. The company plans to develop the compounds to treat autoimmune and inflammatory diseases, including rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). TPTX, which said it sold the assets because they are outside the company’s main focus of CNS disease, will receive equity in CalciMedica and is eligible for sublicense fees, milestones and royalties.

Separately, CalciMedica received exclusive rights to develop therapeutics against the institute’s Oral I, a protein component or regulator of CRAC. Financial terms were not disclosed.

CellCyte Genetics Corp. (CCYG; FSE:LK6), Kirkland, Wash.
Sigma-Aldrich Corp. (SIAL; St. Louis, Mo.
Business: Supply/Service
SIAL’s SAFC Pharma manufacturing unit will supply CCYG with preclinical batches of CCYG’s lead compound, CCG-TH30. The small molecule that helps stem cells target the heart is expected to begin Phase I testing to treat congestive heart failure in Q08. Financial terms were not disclosed.

CellTrend GmbH, Luckenwalde, Germany
Epigenomics AG (FSE:ECX), Berlin, Germany
Myriad Genetics Inc. (MYGN), Salt Lake City, Utah
Business: Pharmacogenetics
ECX will use its Differential Methylation Hybridization DNA microarray platform to screen MYGN’s cancer tissue samples and identify biomarkers associated with sensitivity and resistance to an undisclosed marketed cancer drug. Also, ECX and its service partner CellTrend GmbH will use ECX’s OncoSign approach to identify DNA methylation biomarkers for the drug in a panel of human tumor cell lines. Further terms were not disclosed.

Cortex Pharmaceuticals Inc. (COR), Irvine, Calif.
University of Alberta, Edmonton, Alberta
Business: Neurology, Pulmonary
COR received an exclusive license to the university’s patent application covering the use of an Ampakine compound to treat and prevent opiate- and barbiturate-induced respiratory depression. COR’s Ampakine compounds modulate AMPA-type glutamate receptors. The university will receive undisclosed research funding and an upfront payment and is eligible for milestones and royalties.

CuraMedica Inc., Montreal, Quebec
Mistral Pharma Inc. (TSX-V:MIP), Montreal, Quebec
Business: Neurology
Drug delivery company MIP acquired CuraMedica for about 10 million shares worth about C$500,000 (US$450,000) based on MIP’s close of C$0.05 on May 4, the last trading day before the deal was announced. CuraMedica’s lead product was Instillagel, a gel containing the local anesthetic lidocaine and the anti-septic chlorhexidine to ease discomfort in urology procedures. CuraMedica received exclusive Canadian rights to Instillagel from Farco-Pharma GmbH (Koln, Germany). MIP expects to launch the product, which received Canadian approval May 8, by year end. CuraMedica President Dalal Manoli became MIP’s VP of sales and marketing.

Curis Inc. (CRIS), Cambridge, Mass.
Procter & Gamble Co. (PG), Cincinnati, Ohio
Business: Dermatology
PG will end a 2005 deal to develop CRIS’s Hedgehog agonists as topical treatments for hair growth because the compounds did not demonstrate an acceptable safety profile (see BioCentury, Sept. 26, 2005).

CytoGenix Inc. (CYGX), Houston, Texas
Euрогенетик S.A., Liege, Belgium
Business: Chemistry
CYGX and Euрогенетик signed a letter of intent to develop undisclosed products using CYGX’s synDNA production technology. CYGX has preclinical synDNA vaccines against influenza, HIV/AIDS, smallpox and HBV. Further terms were not disclosed.

Entelos Inc. (LSE:ENTL), Foster City, Calif.
Jubilant BioSys Ltd., Bangalore, India
Business: Computational chemistry/biology, Supply/Service
ENTL will use its PhysioLab in-silico technology to discover and characterize compounds, which Jubilant will develop in undisclosed indications. Rights to resulting compounds will be determined on a case-by-case basis.

Also, the companies will use PhysioLab and Jubilant’s development and clinical capabilities to jointly provide services for predictive biosimulation, modeling, chemistry, biology, preclinical and clinical testing, drug formulation, synthesis, manufacturing and supply. Financial terms were not disclosed.

EvoGenix Ltd. (ASX:EGX), Sydney, Australia
Peptech Ltd. (ASX:PTD; LSE:PTDX), North Ryde, Australia
Business: Antibodies
PTD will acquire fellow antibody company EGX for A$0.15 in cash plus 0.5055 PTD shares for each EGX share, which values the deal at A$1.56 million ($128.1 million), or about A$1.12 per share. The price is a 32% premium to EGX’s close of A$0.85 on May 4, the last trading day before the deal was announced. The cash portion of the deal is A$20.9 million. EGX shareholders will retain a 30% stake in the newco.

The deal gives PTD antibody-engineering technologies including EGX’s Superhumanisation and EvoGene optimization technologies. The newco will develop antibodies for inflammatory diseases, bone diseases and cancer. PTD’s lead program is PN0621, a domain antibody against tumor necrosis factor (TNF) to treat rheumatoid arthritis (RA), psoriatic arthritis, Crohn’s disease, irritable bowel syndrome (IBS) and ankylosing spondylitis. PN0621 is expected to begin Phase I testing this month. EGX’s EGX 010, a modified version of osteoprotegerin, is expected to enter Phase I testing this month.

PTD CEO John Chiplin and Chairman Mel Bridges will retain their titles at the newco, while EGX CEO Merilyn Sleigh will assume a senior advisory role. EGX Chairman Chris Harris will join the newco’s board. The deal is expected to close in August. Citigroup advised PTD, and ABN AMRO Morgans advised EGX.

Evotec AG (FSE:EV), Hamburg, Germany
Panacos Pharmaceuticals Inc. (PANC), Watertown, Mass.
Business: Chemistry, Infectious

See next page
Deals, from previous page

The companies extended and expanded a 2004 collaboration under which EVT uses its medicinal chemistry technologies to identify novel compounds to treat HIV for PANC (see BioCentury, March 29, 2004). Now, EVT also will use its development chemistry technologies to optimize compounds and support the scale-up of selected compounds for development. Financial terms were not disclosed.

Gamida-Cell Ltd., Jerusalem, Israel
NovoThera Ltd., Cambridge, U.K.
Business: Pulmonary, Gene/Cell therapy
The companies will evaluate NovoThera’s automated stem cell expansion and delivery technologies and Gamida-Cell’s StemEx cord blood-derived stem cell expansion technology to design and develop stem cell therapies to treat lung diseases, such as emphysema. NovoThera also will develop animal models and conduct preclinical studies. Ownership of resulting IP will be determined at a later date. Financial terms were not disclosed.

Gemin X Biotechnologies Inc., Montreal, Quebec
Leo Pharma A/S, Ballerup, Denmark
Business: Cancer
Leo granted Gemin X exclusive worldwide rights to develop and market GMX1777 to treat cancer. The small molecule inhibitor of NF-kappa B is in a Phase I trial to treat refractory solid tumors and lymphomas. Leo received an undisclosed upfront payment and is eligible for milestones and royalties.

Gene Logic Inc. (GLGC), Gaithersburg, Md.
Abbott Laboratories (ABT), Abbott Park, Ill.
Business: Pharmaceuticals
GLGC will use its Drug Repositioning Program to reprofile undisclosed compounds from ABT that were discontinued or de-prioritized in clinical testing for reasons other than safety. GLGC is eligible for milestones and royalties on candidates that ABT chooses to pursue. GLGC has an option to exclusively license candidates that ABT chooses not to pursue, in which case ABT would be eligible for milestones and royalties.

Intas Biopharmaceuticals Ltd., Gujarat, India
Viopro Inc. (VPRO), Montreal, Quebec
Business: Biomanufacturing
The companies signed a memorandum of understanding to develop, commercialize and manufacture an undisclosed therapeutic protein. Intas would receive non-exclusive worldwide rights to VPRO’s manufacturing process, the finished products and the active ingredient. VPRO would receive a licensing fee and be eligible for royalties. The companies would share royalties from third-party manufacturers. The deal is expected to finalize in July.

Inverness Medical Innovations Inc. (IMA), Waltham, Mass.
Orange Medical B.V., Tilburg, the Netherlands
Business: Supply/Service
Diagnostic company IMA acquired distributor Orange Medical for €4.2 million ($5.7 million) in cash. IMA said the deal increases its direct distribution network into the Benelux countries.

Isis Pharmaceuticals Inc. (ISIS), Carlsbad, Calif.
Bristol-Myers Squibb Co. (BMY), New York, N.Y.
Business: Cardiovascular
BMY and ISIS partnered to discover, develop and commercialize antisense compounds targeting proprotein convertase subtilisin/kexin 9 (PCSK9), a cholesterol regulator, to prevent and treat cardiovascular disease. BMY will have exclusive, worldwide rights to products from ISIS’s PCSK9 research program, which includes an undisclosed number of compounds. BMY also will use ISIS’s oligonucleotide medicinal chemistry capabilities to identify follow-on PCSK9 antisense compounds with advanced chemistries that BMY said may provide greater potency and oral bioavailability.

The partners will share preclinical development responsibilities, and BMY will be responsible for clinical development and commercialization. ISIS will receive $15 million up front and at least $9 million in research funding over a three-year period. ISIS also is eligible for $168 million in milestones for the first drug candidate and additional milestone for follow-on compounds, plus royalties in the high single-digit to low double-digit range.

KineMed Inc., Emeryville, Calif.
Massachusetts Institute of Technology, Cambridge, Mass.
Business: Cardiovascular
KineMed received options to obtain exclusive rights to MIT’s scavenger receptor class B member 1 (SCARB1, CD36) as a therapeutic target to treat atherosclerosis. The option also covers non-exclusive rights to two SCARB1 knockout mouse models and methods for screening compounds that modulate SCARB1 expression and activity. Financial terms were not disclosed.

Molecular Medicine BioServices Inc., Carlsbad, Calif.
Sigma-Aldrich Corp. (SIAL), St. Louis, Mo.
Business: Biomanufacturing
SIAL acquired contract manufacturing company Molecular Medicine for an undisclosed amount of cash. SIAL said Molecular Medicine’s virus-based vaccine and gene therapy manufacturing capabilities complement SIAL’s SAFc Pharma unit’s transgenic extraction, purification and bacterial fermentation facilities. All of Molecular Medicine’s 60 employees will be retained. SIAL said the deal will bring $12 million in annualized revenues and is expected to be neutral to earnings in 2007. Further terms were not disclosed.

NeuroMedix Inc. (TSX-V:NMX), Toronto, Ontario
Transition Therapeutics Inc. (TSX:TTH), Toronto, Ontario
Business: Neurology
TTH completed its previously announced acquisition of NMX for 6.2 million shares valued at C$10.2 million (US$9.2 million) based on TTH’s close of C$1.65 on May 8, the last trading day before the deal closed (see BioCentury, March 26).

Phenex Pharmaceuticals AG, Ludwigshafen, Germany
Sanofi-aventis Group (Euronext:SAN; SNY), Paris, France
Business: Supply/Service
SAN will evaluate Phenex’s selective nuclear receptor modulator (SNuRM) profiling technology in drug discovery activities. The SNuRM platform identifies and analyzes the selectivity of compounds that act on nuclear receptors. Phenex also will use its panel of nuclear receptor assays to analyze the activity of undisclosed compounds in SAN’s pipeline. Phenex will receive undisclosed fees for the services.

Royalty Pharma, New York, N.Y.
New York University, New York, N.Y.
Business: Autoimmune
Royalty purchased a portion of the university’s royalty interest in Remicade infliximab. The university received $650 million up front and is eligible for sales milestones. The university developed the base IP for
Deals, from previous page

Remicade in collaboration with Centocor Inc., a subsidiary of Johnson & Johnson (JNJ, New Brunswick, N.J.). JNJ and Schering-Plough Corp. (SGP, Kenilworth, N.J.) market the chimeric MAb against tumor necrosis factor (TNF) alpha to treat psoriasis, Crohn’s disease, rheumatoid arthritis (RA) and psoriatic arthritis in the EU, and to treat ankylosing spondylitis, ulcerative colitis, Crohn’s disease, RA and psoriatic arthritis in the U.S. JNJ reported worldwide Remicade sales of $731 million for IQ07 and $3 billion for FY06.

sanofi-aventis Group (Euronext:SAN; SNY), Paris, France
SRI International, Menlo Park, Calif.

Business: Cancer
SRI regained from SAN all rights to tirapazamine. SAN discontinued development of the hypoxic cell sensitizer in February. It was in Phase III testing to treat head and neck cancer, non-small cell lung cancer (NSCLC) and cervical cancer. In 1989, SRI licensed the to Sterling Drugs Inc., now part of SAN.

Stem Cell Innovations Inc. (SCLL), Scotch Plains, N.J.
H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark

Business: ADMET
SCLL will use its C3A human liver cell system to study the hepatic metabolism of an undisclosed set of LUN's compounds to treat CNS disorders. Financial terms were not disclosed.

Viragen Inc. (VRA), Plantation, Fla.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.

Business: Cancer
VRA and the center ended their 1999 deal to develop a human MAb to treat Stage IV malignant melanoma (see BioCentury, Dec. 13, 1999). The center regained the original murine antibody, and the partners will jointly own VG101, the humanized version. The development stage of VG101 is undisclosed.

SALES & MARKETING

Angiotech Pharmaceuticals Inc. (TSE:ANP; ANPI), Vancouver, B.C.
Boston Scientific Corp. (BSX), Natick, Mass.

Business: Cardiovascular
BSX launched its Taxus Express2 paclitaxel-eluting stent to treat coronary artery disease in Japan. ANPI granted BSX a license to use paclitaxel in stents in 1997 (see BioCentury, July 14, 1997).

Axela Biosensors Inc., Toronto, Ontario
BioCheck Inc., Foster City, Calif.

Business: Supply/Service, Diagnostic
Axela received non-exclusive rights to sell BioCheck’s reagents for research and diagnostic applications. Axela plans to market the reagents as disposable assays to be run on Axela’s dotLab multiplex sensor system, which measures protein levels and characterizes protein interactions. BioCheck will supply reagents to Axela and will promote the dotLab sensors, while Axela will promote BioCheck’s plated ELISA kits and other screening products and services. Financial terms were not disclosed.

Beckman Coulter Inc. (BEC), Fullerton, Calif.

Business: Supply/Service
BEC launched its UniCel DxI 600 access immunoassay system, an immunoassay analyzer that will be used with the UniCel chemistry system.

Cytori Therapeutics Inc. (CYTX; FSE:XMPA), San Diego, Calif.
Invitrogen Corp. (IVGN), Carlsbad, Calif.

Business: Supply/Service
IVGN received rights to supply and commercialize CYTX’s adipose-derived stem cell-based products for research purposes. Financial terms were not disclosed.

Expression Pathology Inc., Gaithersburg, Md.
Oridis Biomed GmbH, Graz, Austria

Business: Proteomics
The partners will co-promote Expression’s Liquid Tissue biomarker sample preparation and Director laser microdissection technologies with Oridis’ Tissomics tissue sample screening platform and will collaborate on research projects for biomarker discovery and validation.

Gen-Probe Inc. (GPRO), San Diego, Calif.
Millipore Corp. (MIL), Billerica, Mass.

Business: Supply/Service
The companies expanded a 2005 deal to allow MIL to market and sell GPRO’s Mycoplasma Tissue Culture Non-Isotopic (MTC-NI) test. GPRO developed the MTC-NI test, a DNA probe-based system, prior to the original deal. Under the original deal, the companies partner to exclusively develop, manufacture and commercialize nucleic acid tests for microbiological and virus monitoring of manufacturing processes (see BioCentury, Sept. 5, 2005). The companies expect to launch their first products from the deal this year.

Qiagen N.V. (FSE:QIA; QGEN), Venlo, the Netherlands

Business: Supply/Service
QIA launched its miScript product line to identify multiple miRNAs from one single cDNA reaction in a given biological sample.

OTHER NEWS

Apotex Inc., Weston, Ontario
Bristol-Myers Squibb Co. (BMY), New York, N.Y.
sanofi-aventis Group (Euronext:SAN; SNY), Paris, France

Business: Cardiovascular
BMY and the Antitrust Division of the U.S. Department of Justice reached an agreement in principle to resolve a criminal investigation regarding the proposed settlement of a 2002 lawsuit brought by BMY and SAN against Apotex. BMY agreed to plead guilty to two counts of making false statements to a government agency, for which the maximum fine would be $1 million. The suit, which relates to a generic version of BMY and SAN’s cardiovascular drug Plavix clopidogrel, is pending before the U.S. District Court for the Southern District of New York. The settlement that was proposed last year did not receive antitrust clearance from the state attorneys general (see BioCentury, Aug. 7, 2006).

Atrium Biotechnologies Inc. (TSX:ATB), Quebec City, Quebec

Business: Nutraceuticals
ATB changed its name to Atrium Innovations Inc.

AVI BioPharma Inc. (AVII), Portland, Ore.
U.S. Department of Defense, Washington, D.C.

Business: Infectious
AVII received three contracts totaling $7.1 million from DoD to develop therapeutics against bioterrorism agents. The company will receive $2.7 million to treat Ebola, $2.7 million to treat Marburg virus infections and $1.8 million to treat anthrax and ricin toxin exposure.

See next page
Other News, from previous page

The three preclinical programs use AVI’s Neugene antisense technology. AVI believes it will receive a contract for the fourth program, targeting dengue fever, by year end.

Biofusion plc (LSE:BFN), Sheffield, U.K.
University of Sheffield, Sheffield, U.K.
Business: Infectious

The university spun out Medella Therapeutics Ltd. (Sheffield, U.K.). Medella has exclusive rights to the university’s IP covering MAbs targeting adrenomedullin to treat cancer. The newco has six research-stage candidates. BFN, which invested £320,000 ($640,000) in the company for 60% ownership, commercializes medical-related IP from University of Sheffield and Cardiff University.

Business: Drug delivery

iCeutica spun out Spree Pharma A/S to reformulate and commercialize compounds using iCeutica’s Encapsulated Organic Nanoparticle (EON) reformulation platform. iCeutica also granted Spree exclusive rights to undisclosed compounds, which Spree will reformulate. Spree will be co-owned by iCeutica and venture capital group Nordic Biotech Advisors ApS and located in Copenhagen, Denmark.

Medics Pharmaceutical Corp. (MRX), Scottsdale, Ariz.
Business: Dermatology

MRX will pay the U.S. government $9.8 million to settle allegations that the company violated the False Claims Act by promoting Loprox ciclopirox to treat diaper rash in children under 10. Loprox is approved to treat fungal infections in patients over 10.

Purdue Pharma L.P., Stamford, Conn.
Business: Neurology

Purdue pled guilty in the U.S. District Court for the Western District of Virginia to the felony of misleading the opioid pain drug OxyContin oxycodone and will pay about $600 million in fines and penalties. The company will pay $470 million in fines, penalties and forfeitures to federal and state agencies, as well as $130 million to resolve private civil claims. The U.S. Attorney for the Western District of Virginia alleged that from 1996 to 2001, Purdue employees falsely and misleadingly marketed OxyContin as less addictive, less subject to abuse and less likely to cause withdrawal than other pain medications.

Michael Friedman, president and CEO; Howard Udell, EVP and chief legal officer; and Paul Goldenheim, former EVP, CSO and head of research pled guilty to individual counts of strict liability misdemeanor for their supervisory positions in the company’s marketing practices. Together, the three will pay $34.5 million in penalties and $15,000 in criminal fines.

Arpida Ltd. (SWX:ARPN), Munchenstein, Switzerland
Business: Infectious

Appointed: Michel Pettigrew, COO of Ferring Pharmaceuticals A/S
Departed: Kalid Islam and Soren Carlsen

Atherotech Inc., Birmingham, Ala.
Business: Diagnostic

Appointed: Laura King, former president and CEO of General Electric Co.’s GE Healthcare Interventional Cardiology business unit; and Kenneth Roe, former regional VP and operations leader at Quest Diagnostics Inc.

Auriga Laboratories Inc. (ARGA), Norcross, Ga.
Business: Drug delivery

Appointed: Elliot Maza, president and CFO of Intellect Neurosciences Inc.

Axis-Shield plc (LSE:ASD; OSE:ASD), Dundee, U.K.
Business: Diagnostic

Resigned: Nancy McGoldrick

Biomoda Inc. (BMOD), Albuquerque, N.M.
Business: Diagnostic, Cancer

Appointed: Albert Goodman, former senior scientist at Los Alamos National Laboratories

Biotechnology Industry Organization, Washington
Business: Other

Appointed: Joshua Boger, chairman, president and CEO of Vertex Pharmaceuticals Inc., as chairman; he replaces Biogen Idec Inc.’s President and CEO James Mullen; Joseph Scodari, worldwide chairman of the pharmaceuticals group at Johnson & Johnson, as vice chair of healthcare; Andrew Baum, president and CEO of SemBioSys Genetics Inc, as vice chairman of food and agriculture and secretary; and Mark Skatesky, chairman, president and CEO of Trine Pharmaceuticals Inc., as treasurer

Bradley Pharmaceuticals Inc. (BDY), Fairfield, N.J.
Business: Dermatology, Gastrointestinal

Resigned: Leonard Jacob as non-executive chairman; Seth Hamot, a director, will serve as interim non-executive chairman

Coratus Pharmaceuticals Inc., San Diego, Calif.
Business: Inflammation, Infectious, Metabolic

Appointed: Paul Klingenstein, managing partner at Aberdare Ventures; Patrick Lee, general partner at Advent Venture Partners; William Gerber, partner at Bay City Capital; Marc Perret, senior partner at Gilde Healthcare Partners; and David Hale, chairman of Hale BioPharma Ventures

See next page
Management Tracks, from previous page

Dov Pharmaceuticals Inc. (DOVP), Hackensack, N.J.
Business: Neurology, Cardiovascular
Appointed: Joseph Zakrzewski, CEO and a director of Xcellerex Inc.

Eli Lilly and Co. (LLY), Indianapolis, Ind.
Business: Pharmaceuticals
Hired: Alex Azar II as SVP of corporate affairs and communications, formerly deputy secretary of the U.S. Department of Health and Human Services; he replaces Anne Nobles, who will become chief compliance officer and VP of compliance and enterprise risk management

ExonHit Therapeutics S.A. (Euronext:ALEHT), Paris, France
Business: Neurology, Cancer, Ophthalmic
Appointed: Deborah Smeltzer, VP of operations and CFO of Dynavax Technologies Corp.

ImClone Systems Inc. (IMCL), New York, N.Y.
Business: Cancer
Appointed: Jules Haimovitz, vice chairman and managing partner of Dick Clark Productions Inc.
Resigned: Andrew Bodnar

Indevus Pharmaceuticals Inc. (IDEV), Lexington, Mass.
Business: Genitourinary, Infectious, Endocrine
Appointed: James Gale, managing director at SMH Capital Inc.

Inovio Biomedical Corp. (INO), San Diego, Calif.
Business: Drug delivery
Appointed: Bob Rieder, chairman and CEO of CardioPharma Corp.

Opko Health Inc. (EXEG), Pittsford, N.Y.
Business: Ophthalmic
Hired: Jane Hsiao as vice chairman and chief technology officer, formerly chief technology officer of Ivax Corp.; Steven Rubin as EVP of administration, formerly SVP, general counsel and secretary of Ivax; and Rao Uppaluri as EVP of finance and CFO, formerly treasurer and VP of strategic planning at Ivax
Resigned: Dale Pfost as president

Pharmacoepia Inc. (PCOP), Princeton, N.J.
Business: Cardiovascular, Pulmonary, Autoimmune
Appointed: Martin Soeters, president in U.S. and VP in North America at Novo Nordisk Inc.; and Dennis Langer, managing partner at Phoenix IP Ventures
Departing: James Marino; and Gary Costley

Poniard Pharmaceuticals Inc. (PARD), South San Francisco, Calif.
Business: Cancer
Appointed: Robert Basso, managing partner at Best Partners LLC

Business: Supply/Service, Genomics
Appointed: Salvatore Salamone, chairman and CEO of Saladax BioMedical Inc.

Management

Aeterna Zentaris Inc. (TSX:AEZ; AEZS), Quebec City, Quebec
Business: Endocrine, Infectious, Cancer

Hired: Ellen McDonald as CBO and SVP of business operations, formerly SVP of business operations at Chugai Pharmaceutical Co. Ltd.’s Chugai Pharma USA LLC unit; and Nicholas Pelliccione as SVP of regulatory and pharmaceutical sciences at Chugai Pharma USA

Alltracel Pharmaceuticals plc (LSE:AP), Dublin, Ireland
Business: Dermatology, Drug delivery, Cardiovascular
Hired: Nick Hart as CFO and executive director, formerly CFO of Smart Holograms Ltd.

BioServe Biotechnologies Ltd., Laurel, Md.
Business: Genomics
Hired: Kevin Krenitsky as CEO, formerly CEO of Parkway Clinical Laboratories Inc.; he succeeds Ramakrishna Modali, who will remain president

CellCyte Genetics Corp. (CCYG), Kirkland, Wash.
Business: Gene/Cell therapy
Hired: Nathan McDonald as VP of finance, formerly managing partner at Venture Velocity

CytoCore Inc. (CYCR), Chicago, Ill.
Business: Diagnostic
Hired: Richard Domanik as president

Favrille Inc. (FVRL), San Diego, Calif.
Business: Cancer, Autoimmune
Hired: Richard Ghalie as CMO, formerly VP of medical affairs and professional services at Ligand Pharmaceuticals Inc.

Gilead Sciences Inc. (GILD), Foster City, Calif.
Business: Biopharmaceuticals, Infectious, Pulmonary
Promoted: Paul Carter to SVP of international commercial operations

H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark
Business: Neurology
Hired: Anders Goetzche as CFO and EVP, formerly VP of medical affairs and professional services at Ligand Pharmaceuticals Inc.

La Jolla Pharmaceutical Co. (LJPC), San Diego, Calif.
Business: Autoimmune
Hired: Niv Caviar as EVP, CBO and CFO, formerly VP and head of marketing at Allergan Inc.

Mersana Therapeutics Inc., Cambridge, Mass.
Business: Cancer
Hired: Robert Fram as CMO, formerly VP of clinical development at ImmunoGen Inc.

Parexel International Corp. (PRXL), Boston, Mass.
Business: Supply/Service
Hired: Joe Avellone as VP of operations for clinical research services of the Americas, formerly CEO of Veritas Medicine Inc.

Pharmacyclics Inc. (PCYC), Sunnyvale, Calif.
Business: Cancer, Cardiovascular
Hired: Michael Inouye as SVP of corporate and commercial development, formerly SVP of worldwide commercial operations at Gilead Sciences Inc.

See next page
Clinical activities and selected announcements for the week ended May 11.

**REGULATORY**

**Abbott Laboratories** (ABT), Abbott Park, Ill.
Product: Humira adalimumab
Business: Autoimmune

ABT submitted an sBLA to FDA for Humira to treat juvenile rheumatoid arthritis (RA) in the U.S. and a Type II variation to EMEA to treat juvenile idiopathic arthritis (IA) in the EU. The human monoclonal antibody against TNF alpha is approved to treat RA, psoriatic arthritis and ankylosing spondylitis (AS) in the U.S. and Europe. In April, CHMP issued a positive opinion to expand the label of Humira to include the treatment of severe Crohn’s disease (see BioCentury, April 30). In February, FDA approved an sNDA for Humira to treat moderate to severe active Crohn’s disease (see BioCentury, March 5).

**Amgen Inc.** (AMGN), Thousand Oaks, Calif.
Product: Epogen erythropoietin alpha, Aranesp darbepoeitin alfa
Business: Hematology

FDA’s Oncologic Drugs Advisory Committee recommended in a 15-2 vote that FDA narrow the chemotherapy-induced anemia in cancer patients indication for Aranesp darbepoeitin alfa and Epogen erythropoietin alfa from AMGN and Procrit erythropoietin alpha from Johnson & Johnson (JNJ, New Brunswick, N.J.). The committee also voted 12-5 that FDA should modify the labels on erythropoiesis-stimulating agents (ESAs) to reflect safety signals from trials of the products in specific types of cancer but did not say how the indication should be restricted or which cancer types should be mentioned on the labels. Some ODAC members said FDA should review any proposed label changes with the advisory committee before implementing them. ODAC also voted 15-2 that labels should “define a hemoglobin level in asymptomatic patients at which ESAs should be initiated,” but it did not specify the level. In an 11-6 vote, the committee recommended against lowering the ceiling for hemoglobin elevation from the current 12 g/dL level. It also voted 16-1 to recommend that labels be modified to recommend discontinuation of ESAs following completion of chemotherapy. The panel only made recommendations about oncology indications, but FDA announced that its Cardiovascular and Renal Drugs Advisory Committee will meet in

See next page

**Pharsight Corp.** (PHST), Mountain View, Calif.
Business: Bioinformatics
Hired: Jean-Francois Marier as VP of reporting and analysis services, formerly director of the PK/PD department at MDS Inc.’s MDS Pharma Services Inc. unit

**Poniard Pharmaceuticals Inc.** (PARD), South San Francisco, Calif.
Business: Cancer
Hired: Ronald Martell as president and COO, while remaining a director, formerly SVP of commercial operations at ImClone Systems Inc.; he replaces Jerry McMahon as president, who will remain CEO and chairman

**ProEthic Pharmaceuticals Inc.**, Montgomery, Ala.
Business: Drug delivery
Hired: James Lattanzi as CFO, former consultant and CFO at King Pharmaceuticals Inc.; he will assume the duties of SVP of Finance Joseph Medlin, who will remain COO

**Velcura Therapeutics Inc.**, Ann Arbor, Mich.
Business: Musculoskeletal
Hired: Bill Cadwallader as EVP of corporate development, formerly VP of strategic planning and marketing at Cell Therapeutics Inc.

**Verax Biomedical Inc.**, Worcester, Mass.
Business: Diagnostic
Hired: R. Scott McKenzie as SVP of operations, formerly site director at Abbott Laboratories’ Abbott Diagnostics immunoassay manufacturing unit; and Nancy Hornbaker as VP of regulatory affairs, formerly a regulatory consultant at Biologics Consulting Group Inc.

**ViRexx Medical Corp.** (TSX:VIR; REX), Edmonton, Alberta
Business: Cancer, Infectious
Hired: Peter Smetek Jr. as interim CEO, while remaining chairman; he replaces Lorne Tyrell, who resigned

**Scientific Advisory Boards**

**Array BioPharma Inc.** (ARRY), Boulder, Colo.
Business: Cancer, Inflammation, Chemistry
Appointed: Jonathan Kay, director of clinical trials in the Massachusetts General Hospital rheumatology unit

**IGI Inc.** (IG), Buena, N.J.
Business: Drug delivery
Appointed: Subhash Saxena, partner at JB Consulting Ltd.

**InNexus Biotechnology Inc.** (TSX:IXS; IXSBF), Vancouver, B.C.
Business: Antibodies
Appointed: Thomas Kindt, former director of intramural research and chief of the laboratory of immunogenetics at NIH’s National Institute of Allergy and Infectious Diseases

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the early fall to consider safety issues associated with the use of ESAs in other settings. The drugs also are approved to treat anemia in patients with chronic kidney disease.

Cell Therapeutics Inc. (CTICD; NMerc:CTIC), Seattle, Wash.
Product: Pixantrone
Business: Cancer
FDA granted Fast Track designation for pixantrone to treat relapsed or refractory indolent non-Hodgkin’s lymphoma (NHL). This quarter, CTIC plans to begin the Phase III PIX303 trial of the aza-anthracenedione DNA intercalating agent for the indication. Pixantrone also has Fast Track designation to treat relapsed, aggressive NHL.

Cipher Pharmaceuticals Inc. (TSX:DND), Mississauga, Ontario
Product: Cip-tramadol ER
Business: Neurology
DND received an FDA approvable letter for Cip-tramadol ER to treat pain. The agency noted certain chemistry, manufacturing and controls (CMC) issues and requested an additional clinical trial of the once-daily formulation of tramadol.

Dendreon Corp. (DNDN), Seattle, Wash.
Product: Provenge sipuleucel-T
Business: Cancer
DNDN received an approvable letter from FDA for Provenge sipuleucel-T to treat asymptomatic patients with metastatic, androgen-independent prostate cancer. DNDN said FDA requested additional clinical data to support efficacy, as well as additional information about the CMC section of the application. In March, CBER’s Cellular, Tissue and Gene Therapies Advisory Committee voted 13-4 that DNDN had provided substantial evidence of the efficacy of Provenge. However, apparently leaked letters to FDA from 2 members of FDA’s Oncologic Drugs Advisory Committee who sat on the Provenge panel had started a public debate about whether the product should be approved (see BioCentury, April 30). Provenge is the first cancer vaccine to go before FDA, and the BLA was the first application to be reviewed by the CBER committee (see BioCentury, April 2).

Dor BioPharma Inc. (DORB), Lake Forest, Ill.
Product: orBec beclomethasone dipropionate
Business: Transplant
FDA’s Oncologic Drugs Advisory Committee recommended against approval of orBec beclomethasone dipropionate to treat gastrointestinal graft-versus-host disease (GVHD). ODAC voted 7-2 that the data supporting the corticosteroid did not show substantial evidence of efficacy. The NDA for orBec has a July 21 PDUFA date.

Fabre Kramer Pharmaceuticals Inc., Houston, Texas
GiaxoSmithKline plc (LSE:GSK; GSK), London, U.K.
Product: Gepriron ER
Business: Neurology
Fabre Kramer submitted an amended NDA to FDA for gepriron ER to treat major depressive disorder. The amended application is in response to a 2004 not approvable letter that requested an additional short-term efficacy trial for the serotonin (5-HT1A) receptor agonist (see BioCentury, June 28, 2004). In 2005, the company reported mixed results from a pair of Phase III trials of gepriron ER (see BioCentury, July 4, 2005). In February, Fabre Kramer granted GSK exclusive rights to develop, manufacture and commercialize gepriron ER.

Helsinn Healthcare S.A., Pazzallo, Switzerland
MGI Pharma Inc. (MGN), Bloomington, Minn.
Product: Palonosetron injection
Business: Gastrointestinal
Helsinn submitted an sNDA to FDA for Aloxi palonosetron injection to treat post-operative nausea and vomiting (PONV). MGN markets the serotonin (5-HT3) receptor antagonist in the U.S. to prevent chemotherapy-induced nausea and vomiting (CINV). Aloxi is approved to prevent nausea and vomiting associated with emetogenic cancer chemotherapy in the EU.

IDM Pharma Inc. (IDMI), Irvine, Calif.
Product: Junovan mifamurtide (Mepact-EU)
Business: Cancer
FDA’s Oncologic Drugs Advisory Committee recommended against approval of Junovan mifamurtide to treat newly diagnosed high-grade osteosarcoma. ODAC voted 12-2 that data supporting the muramyl tripeptide phosphatidylethanolamine did not show substantial evidence of efficacy. IDMI expects an FDA decision on the NDA in late August.

Ista Pharmaceuticals Inc. (ISTA), Irvine, Calif.
Product: T-Pred tobramycin/prednisolone
Business: Ophthalmic
ISTA received a not approvable letter from FDA for T-Pred tobramycin/prednisolone to treat steroid-responsive inflammatory ocular conditions where risk of bacterial infection exists. The company plans to request a meeting with FDA to discuss the actions necessary to obtain approval of the topical form of 0.3% tobramycin and 1% prednisolone acetate.

Johnson & Johnson (JNJ), New Brunswick, N.J.
Product: Procrit epoetin alfa
Business: Hematology
FDA’s Oncologic Drugs Advisory Committee voted 15-2 to recommend that FDA narrow the chemotherapy-induced anemia in cancer patients indication for Aranesp darbepoetin alfa and Epogen epoetin alpha from Amgen Inc. (AMGN, Thousand Oaks, Calif.) and Procrit epoetin alpha from JNJ. The committee also voted 12-5 that FDA should modify the labels on erythropoiesis-stimulating agents (ESAs) to reflect safety signals from trials of the products in specific types of cancer but did not say how the indication should be restricted or which cancer types should be mentioned on the labels. Some ODAC members said FDA should review any proposed label changes with the advisory committee before implementing them. ODAC also voted 15-2 that labels should “define a hemoglobin level in asymptomatic patients at which ESAs should be initiated,” but it did not specify the level. In an 11-6 vote, the committee recommended against lowering the ceiling for hemoglobin elevation from the current 12 g/dL level. It also voted 16-1 to recommend that labels be modified to recommend discontinuation of ESAs following completion of chemotherapy. The panel only made recommendations about oncology indications, but FDA announced that its Cardiovascular and Renal Drugs Advisory Committee will meet in the early fall to consider safety issues associated with the use of ESAs in other settings. The drugs also are approved to treat anemia in patients with chronic kidney disease.

Merck & Co. Inc. (MRK), Whitehouse Station, N.J.
Sanofi-aventis Group (Euronext:SAN; SNY), Paris, France
Product: Gardasil
Business: Infectious
Sanofi Pasteur MSD, a joint venture between MRK and SAN, said Sweden will reimburse Gardasil vaccine administered to girls aged 13-18.
17 years. The human papillomavirus (HPV) types 6, 11, 16 and 18 recombinant vaccine is approved in over 70 countries.

MGI Pharma Inc. (MOGN), Bloomington, Minn.
Product: Gliadel Wafer
Business: Cancer
Last month, the U.K.’s National Institute of Health and Clinical Excellence (NICE) recommended in favor of Gliadel carmustine implants to treat newly diagnosed high-grade glioma only in patients whose tumors have been at least 90% resected. NICE withdrew an earlier appraisal recommending against Gliadel to treat newly diagnosed high-grade glioma after the institute discovered a miscalculation in the glioma model used for the appraisal. Archimedes Pharma Ltd. (Reading, U.K.) obtained European rights to the biodegradable polymer implant containing carmustine through its November 2006 acquisition of Link Pharmaceuticals Ltd., which had rights from MOGN.

Mistral Pharma Inc. (TSX-V:MIP), Doval, Quebec
Product: Instillagel
Business: Neurology
Health Canada approved MIP’s Instillagel lidocaine/chlorhexidine gel to ease discomfort during urology procedures. MIP will launch Instillagel in 4Q07. MIP obtained Instillagel when it acquired CuraMedica Inc. earlier this month.

Omrix Biopharmaceuticals Inc. (OMRI), New York, N.Y.
Product: HBIG
Business: Infectious
OMRI submitted a Swedish marketing approval of HBIG, a Hepatitis B immunoglobulin to prevent re-infection of transplanted livers in patients with HBV. The product is approved in Israel.

Schering-Plough Corp. (SGP), Kenilworth, N.J.
Product: Temodar temozolomide (Temodal - EU)
Business: Cancer
The U.K.’s National Institute of Health and Clinical Excellence (NICE) on April 10 recommended Temodar to treat newly diagnosed high-grade glioma in patients with a World Health Organization (WHO) performance status of 0 or 1. NICE withdrew an earlier appraisal recommending Temodar to treat newly diagnosed high-grade glioma in patients with a WHO performance status of 0, but recommending against subsequent use in patients who received it as first-line therapy, after the institute discovered a miscalculation in the glioma model used for the appraisal. In the new appraisal, NICE also recommended Gliadel carmustine implants to treat newly diagnosed high-grade glioma only in patients whose tumors have been at least 90% resected. The biodegradable polymer implant containing carmustine (BCNU) is marketed in the U.S. by MGI Pharma Inc. (MOGN, Bloomington, Minn.) and in Europe by Archimedes Pharma Ltd. (Reading, U.K.).

Schwarz Pharma AG (FSE:SRZ), Monheim, Germany
Product: Neupro rotigotine
Business: Neurology
FDA approved an NDA for Neupro rotigotine to treat early stage Parkinson’s disease (PD). The product is approved in Europe as a monotherapy for early stage PD and as an adjunct to levodopa in advanced stage PD. SRZ is being acquired by UCB Group (Euronext:UCB, Brussels, Belgium).

Somaxon Pharmaceuticals Inc. (SOMX), San Diego, Calif.
Product: Silenor doxepin
Business: Neurology
SOMX said submission of an NDA for Silenor doxepin to treat insomnia might be pushed back to 1Q08 from 3Q07 after FDA requested that results from an ongoing 26-week transgenic mouse carcinogenicity study be included in the initial application. The company had planned to submit the data during the NDA review process. This would be the second delay for the NDA for the low-dose tricyclic doxepin. Additionally, SOMX is still planning to conduct a two-year carcinogenic study previously requested by FDA as a post-approval commitment. FDA requested the additional preclinical work last year (see BioCentury, July 14, 2006).

**CLINICAL RESULTS**

Abbott Laboratories (ABT), Abbott Park, Ill.
Product: ABT-874
Business: Autoimmune
Molecular target: Interleukin-12 (IL-12)
Description: Human monoclonal antibody against interleukin-12 (IL-12)
Indication: Treat psoriasis
Endpoint: Proportion of patients achieving ≥75 response on Psoriasis Area and Severity Index (PASI) at week 12
Status: Additional Phase II data
Milestone: Start Phase III (2007)
Additional data from a double-blind Phase II study in 180 patients showed that >90% of patients in 4 of 5 ABT-874 treatment groups met the primary endpoint of a PASI 75 at week 12 vs. 3% of placebo patients (p<0.001). Also >50% of patients in those treatment groups had a PASI 90 compared with no placebo patients (p<0.001). The 4 treatment groups were: 100 mg of ABT-874 every other week, 200 mg every other week, 200 mg weekly and 200 mg weekly for only 4 weeks. Results were not significant for the 5th treatment group, which received 200 mg of ABT-874 at the start of the study. Data will be presented this week at the Society for Investigative Dermatology meeting in Los Angeles. In January, ABT said the trial met its primary endpoint (see BioCentury, Jan. 29).

Alba Therapeutics Corp., Baltimore, Md.
Product: AT-1001
Business: Autoimmune
Molecular target: Zonulin receptor
Description: Zonulin receptor antagonist
Indication: Treat celiac disease
Endpoint: Intestinal permeability (IP) as measured by the change in urinary lactose to mannitol ratio at Day 14; scores on the Gastrointestinal Symptoms Rating Scale (GSRS) and the Psychological General Well-Being Index (PGWBI)
Status: Preliminary Phase IIa data
Milestone: NA
Preliminary data from a double-blind, placebo-controlled Phase IIa trial in 86 patients showed that AT-1001 did not significantly improve IP at the end of the 14-day trial. However, the IP improvement was significant at day 21, which was 7 days after the end of both dosing and gluteal challenge. GSRS and PGWBI were improved in AT-1001 patients, and Alba said that improvements in “several symptoms and outcomes” were statistically significant. The study enrolled patients on gluten-free diets and a gluten challenge was given 3 times a day.

Alnylam Pharmaceuticals Inc. (ALNY), Cambridge, Mass.
Product: ALN-RSV01

**Clinical Results,**
from previous page

**Business:** Infectious
**Molecular target:** Not available
**Description:** Respiratory syncytial virus (RSV) specific short interfering RNA (siRNA)
**Indication:** Treat and prevent respiratory syncytial virus (RSV)
**Endpoint:** NA
**Status:** NA
**Milestone:** NA

ALNY said its experimental RSV infection model resulted in safe and reliable infections, and the company plans to use the model in a Phase II study of ALN-RSV01 this quarter. The experimental RSV infection study enrolled 36 volunteers who were exposed to RSV. Infection occurred in 72% of subjects. The mean incubation period was 3.2 days and the duration of infection was 7 days. Data were presented at the Pediatric Academic Societies' meeting in Toronto.

**Amgen Inc.** (AMGN), Thousand Oaks, Calif.
**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502), Osaka, Japan

**Wyeth** (WYE), Madison, N.J.
**Product:** Enbrel etanercept
**Business:** Autoimmune
**Molecular target:** Tumor necrosis factor (TNF) alpha; Lymphotoxin (LT) alpha
**Description:** Recombinant p75 TNF receptor linked to the Fc portion of human IgG1 (TNFr:Fc)
**Indication:** Treat, prevent adult rheumatoid arthritis (RA) patients
**Endpoint:** NA
**Status:** Post-marketing study data
**Milestone:** NA

In a Japanese post-marketing surveillance program run by WYE and Takeda, 84.1% of Enbrel patients had a response, as measured by Disease Activity Score 28 (DAS28). The program included 7,091 case reports and the rate of severe side effects was 5.7%. AMGN markets Enbrel in North America while WYE holds rights elsewhere and co-markets the drug in Japan with Takeda.

**Array BioPharma Inc.** (ARRY), Boulder, Colo.
**InterMune Inc.** (ITMN), Brisbane, Calif.
**Roche** (SWX:ROG), Basel, Switzerland

**Product:** ITMN-191
**Business:** Infectious
**Molecular target:** Not available
**Description:** HCV NS3/4A protease inhibitor
**Indication:** Treat hepatitis C virus (HCV) infection
**Status:** Phase Ia data
**Milestone:** Start Phase Ib (3Q07); Phase Ib data (4Q07)

ITMN said ITMN-191 was well tolerated at all dose levels in a double-blind, placebo-controlled, European Phase la trial in about 74 healthy volunteers. Plasma exposure was higher than expected when the compound was dosed with food, which suggests that ITMN-191 could be given at lower doses than were previously estimated. Under a 2006 deal, ROG has exclusive rights to ITMN-191. The compound was discovered under a 2002 HCV deal between ITMN and ARRY.

**Axcan Pharma Inc.** (TSX:AXP, AXCA), Mont St. Hilaire, Quebec
**NicOx S.A.** (Euronext:COX), Sophia-Antipolis, France

**Product:** NCX 1000

**Business:** Cardiovascular
**Molecular target:** NA
**Description:** Nitric oxide-donating derivative of ursodeoxycholic acid (UDCA)
**Indication:** Treat portal hypertension (a late-stage chronic liver disease)
**Endpoint:** Comparison of patients' portal pressure in the fasting state on day 16 with baseline; comparison of patients' portal pressure in the fasting state on day 16 with baseline following the consumption of a controlled meal, response rate (defined in terms of portal pressure reduction), increase in liver blood flow, safety and pharmacokinetics
**Status:** Development discontinued
**Milestone:** NA

The partners will discontinue development of NCX 1000 after preliminary data from 11 evaluable patients in a double-blind, placebo-controlled, dose-escalation, Spanish Phase IIa trial did not show enough efficacy for the treatment of portal hypertension. The partners had been developing NCX 1000 to treat chronic liver diseases under a 2002 collaboration (see BioCentury, May 28, 2002).

**Catalyst Pharmaceutical Partners Inc.** (CPRX), Coral Gables, Fla.
**Product:** CPP-109
**Business:** Neurology
**Molecular target:** NA
**Description:** An irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T)
**Indication:** Treat cocaine addiction
**Endpoint:** NA
**Status:** Phase II data
**Milestone:** NA

In a bioequivalence study in 30 healthy volunteers, a 500 mg tablet of CPP-109 vigabatrin was bioequivalent to a 500 mg tablet of Sabril vigabatrin, which is marketed in Europe by sanofi-aventis Group (Euronext:SAN; SNY, Paris, France) for adult epilepsy and infantile spasms. The compounds had similar maximum plasma concentrations.

**FibroGen Inc.**, South San Francisco, Calif.
**Astellas Pharma Inc.** (Tokyo:4503), Tokyo, Japan

**Product:** FG-2216
**Business:** Hematology
**Molecular target:** Prolyl 4-hydroxylase
**Description:** Small molecule inhibitor of hypoxia-inducible factor-prolyl 4-hydroxylase (HIF-PH)
**Indication:** Treat anemia
**Endpoint:** NA
**Status:** Phase II data
**Milestone:** NA

Astellas said a patient receiving FG-2216 died of fulminant hepatitis in a U.S. Phase II trial to treat anemia. The trial, which is being run by FibroGen, is ongoing and the case has been reported to FDA. Astellas holds exclusive development and marketing rights to FG-2216 in Japan, the EU, the CIS, the Middle East and South Africa under a deal with FibroGen (see BioCentury, May 1, 2006).

**Inspire Pharmaceuticals Inc.** (ISPH), Durham, N.C.
**Boehringer Ingelheim GmbH**, Ingelheim, Germany

**Product:** Intranasal epinastine
**Business:** Inflammation
**Molecular target:** Histamine receptor
**Description:** Intranasal antihistamine
**Indication:** Treat or prevent rhinitis
**Endpoint:** Change from baseline for total nasal symptom score (TNSS)
over 14-day treatment; non-nasal symptom score (watery eyes, itchy eyes, itchy throat) and total symptom score (TNSS plus non-nasal symptom score). Status: Phase II data 
Milestone: NA

In a double-blind, 14-day Phase II trial in 569 patients, a 0.1% dose of epinastine met the primary endpoint of a statistically significant improvement in TNSS vs. placebo (p≤0.05). The 0.05% dose missed the primary endpoint. Patients in the higher dose arm also had statistically significant improvements on secondary endpoints, including non-nasal symptom score and total symptom score vs. placebo (p≤0.05). Boehringer granted ISPH exclusive North American rights to the compound in 2006.

Isotechnika Inc. (TSX:ISA), Edmonton, Alberta 
Roche (SWX:ROG), Basel, Switzerland

Product: Vocllosporin (ISA247, LX2111)
Business: Transplant
Molecular target: Cyclophilin
Description: Transisomer of a cyclosporin analog that inhibits calcineurin
Indication: Prevent renal transplant rejection
Endpoint: Non-inferiority in biopsy proven acute rejection (BPAR) episodes for 6 months compared to tacrolimus; hypertension, hyperlipidemia and new onset diabetes mellitus
Status: Interim Phase IIb data
Milestone: Final Phase IIb data (2008)

Interim 3-month data from 1,16 kidney transplant patients in a Phase IIb trial showed an overall 7% rate of acute rejection in ISA247 patients vs. a 9% rate for patients receiving tacrolimus. The rejection rates for patients receiving 0.4, 0.6 and 0.8 mg/kg of ISA247 twice-daily were 11%, 8% and 3%, respectively. Also, ISA247 patients had improvements in kidney function, as measured by Glomerular Filtration Rate (GFR), that were similar to tacrolimus. There were fewer cases of hypomagnesemia, neurological side effects and new onset diabetes in ISA247 patients compared with the tacrolimus group. ROG has an option to acquire worldwide rights to ISA247 for transplant indications after ISA presents final Phase IIb data.

Ista Pharmaceuticals Inc. (ISTA), Irvine, Calif., 
Senju Pharmaceutical Co. Ltd., Osaka, Japan 
Tanabe Seiyaku Co. Ltd. (Tokyo:4508; Osaka:4508), Osaka, Japan

Product: Bepotastine
Business: Inflammation
Molecular target: Histamine H1 receptor
Description: Eye drop formulation of selective histamine H1 receptor antagonist
Indication: Treat allergic conjunctivitis
Endpoint: Ocular itching and conjunctival redness
Status: Preliminary Phase II/III data
Milestone: File NDA (2H08)

Bepotastine met 1 of 2 primary endpoints in a U.S. Phase II/IIII trial. In the double-blind, placebo-controlled study, both 1% and 1.5% concentrations of the compound, dosed twice-daily significantly reduced ocular itching (p<0.001). However, both concentrations missed the other primary endpoint of a significant reduction in ocular redness. Senju has exclusive worldwide rights to bepotastine, excluding certain Asian countries, from Tanabe, which markets the compound in Japan to treat allergic rhinitis and urticaria. Senju granted ISTA exclusive North American rights to the compound last year.

Johnson & Johnson (JNJ), New Brunswick, N.J. 
Product: CoStar
Business: Cardiovascular
Molecular target: Not applicable
Description: Cobalt chromium paclitaxel drug-eluting stent
Indication: Treat de novo lesions in patients with single or multiple vessel coronary artery disease (CAD)
Endpoint: Major adverse cardiac events (MACE) at 8 months, defined as a composite of target vessel revascularization (TVR), myocardial infarction (MI) and cardiac-related death; target lesion revascularization (TLR), binary restenosis, in-segment and in-stent late loss
Status: Development discontinued
Milestone: NA

JNJ’s Conor Medsystems LLC unit discontinued development of CoStar after the stent missed the primary endpoint of a MACE rate at 8 months that was non-inferior to Taxus Express 2 in the pivotal COSTAR II trial in about 1,700 patients. JNJ also said it and its partners will stop selling CoStar in certain countries in Europe, Asia and Latin America, where it already is approved. Taxus Express 2 is a paclitaxel drug-eluting stent marketed by Boston Scientific Corp. (BSX, Natick, Mass.). Data from COSTAR II will be presented at the EuroPCR meeting in Barcelona this month.

Merck & Co. Inc. (MRK), Whitehouse Station, N.J. 
sanofi-aventis Group (Euronext:SAN; SNY), Paris, France
Product: Gardasil
Business: Infectious
Molecular target: Not applicable
Description: Human papillomavirus (HPV) types 6, 11, 16 and 18 recombinant vaccine
Indication: Prevent human papillomavirus (HPV) infection
Endpoint: Combined incidence of HPV 16/18-related CIN 2/3, adenocarcinoma in situ (AIS) or cancer
Status: Phase III data
Milestone: NA

In the double-blind, placebo-controlled, international Phase III FUTURE I trial, Gardasil was 100% effective in preventing cervical, vaginal and vulvar diseases caused by HPV types 6, 11, 16 and 18 after an average follow-up of 3 years. There were no cases of genital warts or vulvar and vaginal external lesions and pre-cancers in the Gardasil group vs. 60 cases in placebo patients. Data were published in The New England Journal of Medicine.

Indication: Prevent human papillomavirus (HPV) infection
Endpoint: Combined incidence of HPV 16/18-related CIN 2/3, adenocarcinoma in situ (AIS) or cancer
Status: Phase III data
Milestone: NA

MRK published previously reported data from the double-blind, placebo-controlled Phase III FUTURE II trial in 10,559 evaluable patients showing that Gardasil was 98% effective in preventing high-grade pre-cancers associated with HPV types 16 and 18. Results were published in The New England Journal of Medicine. Data from FUTURE II trial were originally announced in 2005 (see BioCentury, Oct. 10, 2005).

Pacgen Biopharmaceuticals Corp. (TSX-V:PGA), Vancouver, B.C.
Product: PAC-113
Business: Infectious
Molecular target: NA
Description: Oral mouth rinse composed of an amphipathic molecule derived from a naturally occurring histatin protein that interacts with fungal cell membranes and mitochondria

See next page
Indication: Treat oral candidiasis
Endpoint: Safety, tolerability; efficacy of mouth rinse in eliminating clinical signs and symptoms of infection, microbiological response
Status: Phase I/II data

Milestone: Final Phase I/II data (2Q07); start Phase I (4Q07)

In a Phase I/II trial in >100 HIV seropositive patients with oral candidiasis, PAC-113 mouth rinse was safe, well tolerated and had clinical cure rates that were comparable to Nystatin oral suspension, the standard of care. At the end of the 14-day treatment phase of the U.S. and South African trial, 37% of PAC-113 patients were clinically cured vs. 36% of Nystatin patients. Complete or partial responses were seen in 95% of PAC-113 patients vs. 87% of Nystatin patients. The top line data were from patients who were at least 80% compliant in the treatment phase.

Pozen Inc. (POZN), Chapel Hill, N.C.
GlaxoSmithKline plc (LSE:GSK; GSK), London, U.K.
Product: Trexima sumatriptan/naproxen
Business: Neurology
Molecular target: Serotonin (5-HT1B) receptor; Serotonin (5-HT1D) receptor
Description: Combination of sumatriptan and naproxen sodium
Indication: Treat acute migraine
Endpoint: Percentage of patients with headache relief 2 hours after dosing, absence of photophobia and absence of phonophobia, absence of nausea
Status: Additional Phase III data
Milestone: NA

Data from the subset of 1,100 patients from 2 double-blind, U.S. Phase III trials (Study 1 and Study 2) in a total of 2,956 patients showed that Trexima significantly lowered the incidence of non-traditional migraine-associated symptoms at 2 and 4 hours vs. placebo. At 2 hours, Trexima reduced sinus pain/pressure by 14% and neck pain/discomfort by 10% vs. placebo. At 4 hours, Trexima reduced sinus pain/pressure by 16% and neck pain/discomfort by 16% vs. placebo. Data were presented at the American Academy of Neurology meeting in Boston. Last month, data from the trials were published in the Journal of the American Medical Association and showed that Trexima significantly improved several traditional migraine-associated symptoms vs. placebo (see BioCentury, April 9).

Repligen Corp. (RGEN), Waltham, Mass.
Product: Secretin (RG1068)
Business: Diagnostic
Molecular target: Unknown
Description: Synthetic human secretin
Indication: Aid in functional magnetic resonance imaging (MRI) of the pancreas
Endpoint: NA
Status: Phase II data
Milestone: NA

In a Phase II trial in 80 patients with a history of pancreatitis, RG1068 plus MRI improved the detection of structural abnormalities of the pancreatic duct by 20% vs. MRI alone. The combination also significantly improved physician’s confidence in identifying abnormalities, the number of visualized duct segments and overall image quality.

Roche (SWX:ROG), Basel, Switzerland
Product: CellCept mycophenolate mofetil (R99)
Business: Transplant
Molecular target: Inosine monophosphate dehydrogenase (IMPDH)

Description: Reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH)
Indication: Prevent renal transplant rejection
Endpoint: Superior glomerular filtration rate (GFR) at 12 months post-transplant, non-inferior biopsy-proven acute rejection (BPAR), graft survival, patient survival at 12 months; acute rejection episodes, BPAR, treatment for rejection, rejection episodes, time to first acute rejection, incidence of treatment failure and safety
Status: Phase IV data
Milestone: NA

In the open-label Phase IV Spare the Nephron (STN) trial in 305 renal transplant patients, the rate of BPAR at 12 months of follow-up was 6.1% for patients receiving CellCept plus sirolimus vs. 7.3% for CellCept plus a calcineurin inhibitor. Also, graft loss occurred in 2% of patients in the CellCept plus sirolimus group vs. 3.6% in the other group. Data were presented at the American Transplant meeting in San Francisco.

Sequenom Inc. (SQNM), San Diego, Calif.
Product: Rhesus D Genotyping Assay
Business: Diagnostic
Molecular target: Not applicable
Description: Fetal Rhesus D (RhD) genotyping assay
Indication: Detect prenatal RhD incompatibility
Endpoint: NA
Status: Feasibility study data
Milestone: NA

In a feasibility study comparing SQNM’s fetal RhD genotyping assay with real-time PCR, both methods produced 100% sensitivity and 98% specificity. The study examined samples from 100 women who were 13-39 weeks pregnant.

Argos Therapeutics Inc., Durham, N.C.
Beckman Coulter Inc. (BEC), Fullerton, Calif.
Product: Soluble CD83
Indication: Prevent graft rejection

In mice with heart transplants, monotherapy with sCD83 produced graft survival of 15 days vs. 8.3 days for control animals. Animals receiving sCD83 plus anti-CD45RB MAb and rapamycin had graft survival of >100 days. Data were presented at the American Transplant meeting in San Francisco. Argos has an exclusive license from BEC to develop and commercialize the soluble CD83 (sCD83) protein with immunosuppressive properties for therapeutic uses (see May 1, 2006).

4SC AG (FSE:VSC), Martinsried, Germany
Product: SC75741
Indication: Treat influenza virus

VSC said its SC75741 was effective in treating mice infected with avian influenza.

GenVec Inc. (GNVC), Gaithersburg, Md.
Product: Ad35 vector
Indication: Treat age-related macular degeneration (AMD)

In mice, intravitreous injections of Ad35 vector showed 4 months of sustained protein expression. Green fluorescent protein (GFP) was used as the expression marker. GNVC said the gene delivery system could be used to deliver therapeutic proteins to the eye in patients with wet AMD or other ocular neovascular diseases. Data were presented at the Association for Research in Vision and Ophthalmology meeting in Fort Lauderdale.
Preclinical Results,
from previous page

LigoCyte Pharmaceuticals Inc., Bozeman, Mont.
Product: Influenza virus-like particles (VLPs)
Indication: Prevent influenza virus
In mice, LigoCyte’s influenza VLPs provided 100% protection against challenge with H1N1 and H3N2 influenza viruses. Data were presented at the Vaccine Research meeting in Baltimore.

Quest PharmaTech Inc. (TSX-V:QPT), Edmonton, Alberta
Product: SL-052
Indication: Treat prostate cancer
In multiple animal models, photodynamic therapy with SL-052 selectively destroyed cancerous prostate tissue and shut down the metabolic activity of tumors within 24 hours. SL-052 is an injectable formulation of HB derivative used with photodynamic therapy.

CLINICAL STATUS

Aastrom Biosciences Inc. (ASTM), Ann Arbor, Mich.
Product: Tissue Repair Cells (TRCs)
Business: Musculoskeletal
Molecular target: Not applicable
Description: TRCs made from bone marrow containing adult stem cells using the AastromReplicell System
Indication: Treat osteonecrosis
Endpoint: Prevent or delay the progression of osteonecrosis to fracturor collapse of femur head as measured through MRI and CT imaging
Status: Phase III start
Milestone: Start Phase III (2007)
This year, ASTM will begin a double-blind, U.S. Phase III trial in 120 patients with osteonecrosis of the femoral head. Patients will have a core track drilled into the head of their femur in order to relieve internal pressure, after which bone matrix carrier with or without TRCs will be administered into the track.

Abraxis BioScience Inc. (ABBI), Los Angeles, Calif.
Product: Nab-docetaxel (ABI-008)
Business: Cancer
Molecular target: NA
Description: Microtubule stabilizer
Indication: Treat hormone refractory prostate cancer
Endpoint: Safety and anti-tumor activity
Status: Phase I/II started
Milestone: NA
ABI-008 began a U.S. Phase I/II trial of ABI-008 dosed once every 3 weeks.

Achillion Pharmaceuticals Inc. (ACHN), New Haven, Conn.
Product: Elvucitabine (ACH-443, beta-L-Fd4C, ACH-126)
Business: Infectious
Molecular target: Viral polymerase
Description: Nucleoside analog viral polymerase inhibitor
Indication: Treat HIV infection/AIDS
Endpoint: Virologic response, safety; pharmacokinetics, efficacy as measured by the change in HIV-1 RNA and helper T cell (CD4) count
Status: Completed Phase II enrollment
Milestone: Phase II data (2007)
ACHN completed enrollment of 78 treatment-naive patients in a double-blind, U.S. Phase II trial comparing elvucitabine to lamivudine when each is used in combination with efavirenz and tenofovir. Epivir lamivudine is marketed by GlaxoSmithKline plc (LSE:GSK; GSK, London, U.K.); Stocrin/Sustiva efavirenz is marketed by Bristol-Myers Squibb Co. (BMY, Princeton, N.J.) and Merck & Co. Inc. (MRK, Whitehouse Station, N.J.) and Viread tenofovir by Gilead Sciences Inc. (GILD, Foster City, Calif.).

Alba Therapeutics Corp., Baltimore, Md.
Product: AT-1001
Business: Autoimmune
Molecular target: Zonulin receptor
Description: Zonulin receptor antagonist
Indication: Treat celiac disease
Endpoint: Composite index of disease activity
Status: Phase IIb start
Milestone: Start Phase IIb (3Q07); complete Phase IIb (early 2008)
Next quarter, Alba will begin a U.S. and Canadian Phase IIb trial.

Alkermes Inc. (ALKS), Cambridge, Mass.
Indevus Pharmaceuticals Inc. (IDEV), Lexington, Mass.
Product: ALKS 27
Business: Pulmonary
Molecular target: Muscarinic receptors
Description: Inhaled formulation of tropsium chloride, a muscarinic receptor antagonist
Indication: Treat chronic obstructive pulmonary disease (COPD)
Endpoint: Safety, tolerability and pharmacokinetics
Status: Phase IIa started
Milestone: Phase IIa data (2H07)
Last month, the partners began a double-blind, placebo-controlled, crossover, U.S. Phase IIa trial in 24 patients. ALKS and IDEV are co-developing the product under a 2005 deal.

Altus Pharmaceuticals Inc. (ALTU), Cambridge, Mass.
Product: ALTU-135
Business: Gastrointestinal
Molecular target: Not available
Description: Cross-linked pancreatic enzyme crystals
Indication: Treat malabsorption due to exocrine pancreatic insufficiency in chronic pancreatitis or cystic fibrosis (CF) patients
Endpoint: Safety
Status: Phase III start
Milestone: Start Phase III (2Q07); Phase III data (2009)
This quarter, ALTU hopes to begin the open-label, single-arm, international Phase III (DIGEST safety) trial of oral ALTU-135 in about 240 patients with either CF or chronic pancreatitis. ALTU-135 has Orphan Drug designation from FDA and EMEA and Fast Track designation from FDA.
Indication: Treat malabsorption due to exocrine pancreatic insufficiency in cystic fibrosis (CF) patients
Endpoint: Improvement of fat absorption; protein absorption, carbohydrate absorption and stool weight frequency
Status: Phase III started
Milestone: Phase III data (2Q08)
ALTU began the double-blind, placebo-controlled, international Phase III (DIGEST efficacy) trial of oral ALTU-135 in about 150 CF patients ages 7 and up. ALTU-135 has Orphan Drug designation from FDA and EMEA and Fast Track designation from FDA.

Ambrilia Biopharma Inc. (TSX:AMB), Verdun, Quebec
Product: Goserelin
Business: Cancer
**Clinical Status**, from previous page

Molecular target: GnRH/LHRH receptor
Description: 12-week formulation of goserelin, a leutinizing hormone-releasing hormone (LHRH) analog
Indication: Treat hormone-sensitive prostate cancer
Endpoint: Pharmacokinetics, testosterone levels; safety; tumor markers and radiographic changes
Status: Phase I/II start
Milestone: Start Phase I/II (2007); Phase I/II data (mid-2008)

This year, AMB will begin an open-label, European Phase I/II trial in 12-24 patients to evaluate a subcutaneous biodegradable implant of Goserelin.

Product: Octreotide
Business: Endocrine
Molecular target: Growth hormone receptor
Description: Prolonged-release formulation of Octreotide
Indication: Treat acromegaly
Endpoint: Efficacy compared to Sandostatin LAR based on IGF-I and GH levels; safety
Status: Phase III started
Milestone: Phase III data (early 2008)

Last quarter, AMB began an open-label, European Phase III trial in about 60 patients to compare intramuscular Octreotide to Sandostatin LAR from Novartis AG (NVS; SWX:NOVN, Basel, Switzerland).

**Array BioPharma Inc.** (ARRY), Boulder, Colo.

**InterMune Inc.** (ITMN), Brisbane, Calif.

**Roche** (SWX:ROG), Basel, Switzerland
Product: ITMN-191
Business: Infectious
Molecular target: Not available
Description: HCV NS3/4A protease inhibitor
Indication: Treat hepatitis C virus (HCV) infection
Endpoint: Safety, viral kinetics
Status: Phase Ib start
Milestone: Start Phase Ib (3Q07); Phase Ib data (4Q07)

Next quarter, ITMN will begin the Phase Ib MAD trial in patients with chronic HCV genotype 1 infection. The 14-day trial will evaluate oral ITMN-191 as monotherapy. Last year, ROG gained exclusive rights to the agent, which was discovered by ITMN and ARRY under a 2002 HCV deal.

**Bavarian Nordic A/S** (CSE:BAVA), Copenhagen, Denmark
Product: MVA-BN Prostate cancer vaccine
Business: Cancer
Molecular target: NA
Description: Modified Vaccinia ankara (MVA) vector vaccine against prostate specific antigen (PSA) and prostatic acid phosphatase (PAP)
Indication: Treat prostate cancer
Endpoint: N/A
Status: Phase I start
Milestone: Start Phase I (year end 2007)

This year, BAVA’s BN ImmunoTherapeutics Inc. subsidiary will start a Phase I trial.

**BioCryst Pharmaceuticals Inc.** (BCRX), Birmingham, Ala.

**Mundipharma International Ltd.**, Cambridge, U.K.
Product: Fodosine forodesine hydrochloride
Business: Cancer
Molecular target: Purine nucleoside phosphorylase
Description: Purine nucleoside phosphorylase (PNP) inhibitor
Indication: Treat cutaneous T cell lymphoma (CTCL)
Endpoint: NA
Status: Phase IIa start
Milestone: Start Phase IIa (3Q07)

Next quarter, BCRX will begin a pivotal Phase IIb trial in patients refractory to cenic therapies. BCRX granted Mundipharma exclusive rights to Fodosine in Europe, Australia, New Zealand and certain Asian countries.

**BioCryst Pharmaceuticals Inc.** (BCRX), Birmingham, Ala.

**Roche** (SWX:ROG), Basel, Switzerland
Product: BCX-4208
Business: Autoimmune
Molecular target: Purine nucleoside phosphorylase
Description: Second-generation purine nucleoside phosphorylase (PNP) inhibitor
Indication: Treat psoriasis
Endpoint: NA
Status: Phase IIa start
Milestone: Start Phase IIa (3Q07)

Next quarter, the partners will begin a Phase IIa trial. BCX-4208 is partnered with ROG for transplant and autoimmune diseases.

**Biogen Idec Inc.** (BIIB), Cambridge, Mass.

**Vernalis plc** (LSE:VER), Winnersh, U.K.
Product: BIIB014 (formerly V2006)
Business: Neurology
Molecular target: Adenosine A2A receptor
Description: Adenosine A2A receptor antagonist
Indication: Treat late-stage Parkinson’s disease
Endpoint: Safety and tolerability; evaluation of motor functions, pharmacokinetics
Status: Phase II started
Milestone: Phase II data (2008)

BIIB began a double-blind, placebo-controlled Phase II trial in 100 patients to evaluate single and repeated doses of BIIB014 plus levodopa.
over 8 weeks. BIIB licensed exclusive rights to the compound from VER in 2004.

Indication: Treat early-stage Parkinson’s disease
Endpoint: Safety and tolerability; evaluation of motor functions, pharmacokinetics
Status: Phase II start
Milestone: Start Phase II (mid-2007); Phase II data (2008)

This summer, BIIB plans to begin a double-blind, placebo-controlled, dose-ranging Phase II trial in 40 patients. BIIB licensed exclusive rights to the compound from VER in 2004.

Boehringer Ingelheim GmbH, Ingelheim, Germany
Product: Viramune nevirapine
Business: Infectious
Molecular target: Viral polymerase
Description: Non-nucleoside reverse transcriptase inhibitor
Indication: Prevent perinatal HIV transmission
Endpoint: Virologic response defined as viral load of <50 copies/mL after 48 weeks
Status: Phase IIIb started
Milestone: NA

The company began the open-label, international Phase IIIb ArTEN trial in 561 treatment-naïve HIV patients to compare once- or twice-daily Viramune plus tenofovir to once-daily atazanavir/ritonavir plus tenofovir. Viread tenofovir is marketed by Gilead Sciences Inc. (GILD, Foster City, Calif.).

Cell Genesys Inc. (CEGE), South San Francisco, Calif.
Product: GVAX vaccine for leukemia
Business: Cancer
Molecular target: Not applicable
Description: Allogeneic cancer vaccine engineered to secrete granulocyte macrophage-colony stimulating factor (GM-CSF) plus irradiated autologous cells
Indication: Treat myelodysplastic syndrome (MDS)
Endpoint: Safety, hematologic and cytogenetic response; immune response and correlation with clinical endpoints and WT-1 biomarker response
Status: Phase I started
Milestone: NA

CEGE began an open-label, U.S. Phase I trial in 18 patients with poor risk MDS.

Indication: Treat chronic myelogenous leukemia (CML)
Endpoint: Bcr-Abl molecular response, safety; immune response, comparison of response between initial treatment course and boost treatment course
Status: Extension study started
Milestone: NA

CEGE began an extension study of an open-label, U.S. Phase II trial to evaluate a second course of intradermal GVAX in 11 patients who responded to the first course but failed to achieve a sustained complete response.

Indication: Treat chronic myelogenous leukemia (CML)
Endpoint: Progression-free survival at 1 year in patients with complete Bcr-Abl molecular response following cessation of therapy; molecular complete response rates
Status: Phase II started

Milestone: NA

CEGE began an open-label, U.S. Phase II trial in 56 patients with persistent CML following Gleevec therapy. The trial will compare intradermal GVAX plus Gleevec to Gleevec plus interferon alpha and GM-CSF. Gleevec imatinib is marketed by Novartis AG (NVS; SWX:NOVN, Basel, Switzerland).

CombinatorRx Inc. (CRXX), Cambridge, Mass.
Product: CRx-150
Business: Autoimmune
Molecular target: Not available
Description: Syncretic compound containing low doses of amoxapine and dipyridamole
Indication: Treat rheumatoid arthritis (RA)
Endpoint: Reduction of C-reactive protein (CRP), ACR20 score
Status: Completed Phase II enrollment
Milestone: Phase II data (2Q07)

CRXX completed enrollment of 64 patients in a placebo-controlled, European Phase II trial.

Corcept Therapeutics Inc. (CORT), Menlo Park, Calif.
Product: Corlux mifepristone
Business: Neurology
Molecular target: Progesterone receptor; Cortisol receptor GR-2
Description: Small molecule antiprogestin
Indication: Treat psychotic features of psychotic major depression (PMD)
Endpoint: NA
Status: Phase III start
Milestone: Start Phase III (2007)

This year, CORT will begin a Phase III trial to evaluate 1,200 mg once-daily Corlux for 7 days.

Critical Therapeutics Inc. (CRTX), Lexington, Mass.
Product: Zileuton CR
Business: Inflammation
Molecular target: 5-lipoxygenase
Description: Controlled-release formulation of 5-lipoxygenase inhibitor
Indication: Treat asthma
Endpoint: NA
Status: NA
Milestone: NA

This quarter, CRTX will begin a trial of zileuton CR as an add-on therapy to moderate doses of inhaled corticosteroids. The product has a May 31 PDUFA date to prevent and treat asthma in patients ages 12 and up.

Product: Zileuton IV
Business: Inflammation
Molecular target: 5-lipoxygenase
Description: Intravenous formulation of 5-lipoxygenase inhibitor
Indication: Treat acute asthma attack
Endpoint: NA
Status: Phase II start
Milestone: Start Phase II (2H07)

Next half, CRTX will begin a Phase II trial in patients experiencing acute exacerbations of asthma and other acute hospital-based pulmonary conditions.

Emergent BioSolutions Inc. (EBS), Rockville, Md.
Product: Typhoid vaccine
BioCentury Part II

**Clinical Status, from previous page**

**Ipsen Group** (Euronext:IPN), Paris, France
Product: Somatuline Autogel
Business: Endocrine
Molecular target: Somatostatin receptor
Description: Extended-release formulation of somatostatin analog lanreotide
Indication: Treat acromegaly
Endpoint: Percentage of subjects or their partners that are competent at self-administration at the end of the study as assessed by the competence questionnaire score; percentage of switch subjects who find self-administration convenient
Status: Phase IV started
Milestone: NA

TRCA began the open-label, U.S. Phase IV SALSA trial in 60 patients who will self-assess the ease of administering Somatuline Autogel over a 7-month period. IPN granted TRCA exclusive rights to develop and market Somatuline Autogel in the U.S. and Canada (see BioCentury, July 24, 2006).

**Gemin X Biotechnologies Inc.**, Montreal, Quebec
Product: GMX1777
Business: Cancer
Molecular target: NA
Description: Small molecule pro-apoptotic inhibitor of NF-kappa B
Indication: Treat refractory lymphomas
Endpoint: Pharmacokinetics and anti-tumor activity
Status: Phase I started
Milestone: NA

Gemin X started an open-label, dose-escalation Phase I trial of intravenous GMX1777 in 18-24 patients with refractory solid tumors and lymphomas. Last week, Gemin X licensed exclusive worldwide rights to the compound from Leo Pharma A/S (Ballerup, Denmark).

Indication: Treat refractory solid tumors
Endpoint: Pharmacokinetics and anti-tumor activity
Status: Phase I started
Milestone: NA

Gemin X started an open-label, dose-escalation Phase I trial of intravenous GMX1777 in 18-24 patients with refractory solid tumors and lymphomas. Last week, Gemin X licensed exclusive worldwide rights to the compound from Leo Pharma A/S (Ballerup, Denmark).

**ImmunoCellular Therapeutics, Ltd.** (IMUC), Los Angeles, Calif.
Product: Brain tumor vaccine
Business: Cancer
Molecular target: NA
Description: A vaccine derived from dendritic cells cultured with antigens specific to brain tumor cells
Indication: Brain cancer
Endpoint: Safety, toxicity, immune response
Status: Phase I started
Milestone: NA

IMUC started a U.S. Phase I trial in about 30 patients.

**Inspire Pharmaceuticals Inc.** (ISPH), Durham, N.C.
Product: INS115644
Business: Ophthalmic
Molecular target: NA
Description: Ophthalmic solution of a compound that acts to disrupt formation of certain structures in the trabeculum
Indication: Treat glaucoma
Endpoint: Safety, tolerability, change in intraocular pressure
Status: Phase I started
Milestone: Phase I data (4Q07)

In March, ISPH began a double-blind, placebo-controlled, ascending-dose Phase I trial in 42 patients with bilateral ocular hypertension or early, primary open-angle glaucoma.

**BioCentury Extra: Online every business day.**
Clinical Status,
from previous page

Molecular target: Unknown
Description: Small molecule cardioprotectant
Indication: Reduce cardiovascular events in patients undergoing coronary artery bypass graft (CABG) surgery
Endpoint: Reduction in the composite of non-fatal myocardial infarction (MI) and cardiovascular death at post-operative day (POD) 30
Status: Phase III ongoing
Milestone: Complete Phase III enrollment (11/2007)

An independent data safety monitoring board (DSMB) recommended continuation of the double-blind, placebo-controlled, North American and European Phase III MEND-CABG II trial in about 3,000 patients undergoing CABG surgery. MC-1 has Fast Track designation for the indication.

MedImmune Inc. (MEDI), Gaithersburg, Md.
Micromet Inc. (MITI), Bethesda, Md.
Product: MT103 (formerly MEDI-538)
Business: Cancer
Molecular target: CD19; CD3
Description: Bispecific T cell engager (BiTE) that combines epitopes recognizing the CD3 and CD19 surface antigens
Indication: Treat acute lymphoblastic leukemia (ALL)
Endpoint: NA
Status: Phase II start
Milestone: Start Phase II (2007)

This year, the partners will begin a European Phase II trial. MEDI licensed North American rights to MT103 from MITI in 2004 (see BioCentury, June 15, 2004).

Indication: Treat non-Hodgkin’s lymphoma
Endpoint: NA
Status: NA
Milestone: NA

This year, the partners will begin a U.S. trial. MEDI licensed North American rights to MT103 from MITI in 2004 (see BioCentury, June 15, 2004).

Merck Serono S.A. (SWX:SEO), Geneva, Switzerland
Micromet Inc. (MITI), Bethesda, Md.
Product: Adecatumumab (MT201)
Business: Cancer
Molecular target: Epithelial cell adhesion molecule (EpCAM)
Description: Human monoclonal antibody against the EpCAM antigen
Indication: Treat solid tumors
Endpoint: NA
Status: Phase I start
Milestone: Start Phase I (2007)

This year, the partners will begin a Phase I trial. MITI partnered the product with SEO in 2004.

Molecular Insight Pharmaceuticals Inc. (MIPI), Cambridge, Mass.
Product: Azedra
Business: Cancer
Molecular target: Norepinephrine transporter
Description: Reduced cold carrier-radiolabeled norepinephrine analog
Indication: Treat malignant pheochromocytoma
Endpoint: Maximum tolerated dose (MTD) and objective tumor response at 9 months; response rate at 3, 6 and 12 months, biochemical response rate
Status: Phase I/II started

Milestone: NA
MIPI began an international Phase I/II trial that will initially enroll 12-18 patients to determine the MTD of intravenous Azedra. The second portion will then enroll up to 37 patients.

Neuren Pharmaceuticals Ltd. (ASX:NEU), Auckland, New Zealand
Product: NNZ-2566
Business: Inflammation
Molecular target: Not available
Description: Small molecule analog of glycine-proline-glutamate, which is derived from insulin-like growth factor-1 (IGF-1) but does not bind to IGF-1 receptors
Indication: Treat severe traumatic brain injury (TBI)
Endpoint: Mortality and neurological function; biochemical and electroencephalographic markers
Status: Phase IIa start
Milestone: Start Phase IIa (1Q08); complete Phase IIa (year end 2008)

In 1Q08, NEU will begin an open-label, U.S. Phase IIa trial in 40-50 patients.

Indication: Treat severe traumatic brain injury (TBI)
Endpoint: Mortality, Glasgow outcomes score
Status: Phase IIb start
Milestone: Start Phase IIb (2H08); complete Phase IIb (2009)

Next year, NEU will begin a double-blind, placebo-controlled, international Phase IIb trial in about 200 patients.

Indication: Treat mild to moderate traumatic brain injury (TBI)
Endpoint: Neuropsychological and neurocognitive function
Status: Phase II start
Milestone: Start Phase II (2H07); complete Phase II (2008)

Next half, NEU will begin a placebo-controlled, Australian and New Zealand Phase II trial in 60-70 patients to evaluate a bolus of NNZ-2566 followed by an IV infusion for 12-24 hours.

Omrix Biopharmaceuticals Inc. (OMRI), New York, N.Y.
Product: Adhexil
Business: Musculoskeletal
Molecular target: NA
Description: Anti-adhesion
Indication: Prevent post-operative adhesions
Endpoint: NA
Status: Phase I/II start
Milestone: Start Phase I/II (1H07)

This half, OMRI will begin a Phase I/II trial in patients undergoing laparoscopic surgery.

Oramed Pharmaceuticals Inc. (ORMP), Jerusalem, Israel
Product: Oramed Insulin Capsule
Business: Endocrine
Molecular target: NA
Description: Oral insulin
Indication: Treat diabetes
Endpoint: Safety
Status: Phase I started
Milestone: Phase I data (2008)
ORMP began an Israeli Phase I trial in 8 healthy volunteers.

Pharmos Corp. (PARS), Iselin, N.J.
Product: NanoEmulsion diclofenac topical cream
Business: Neurology
Molecular target: NA

See next page
**Clinical Status, from previous page**

Description: Non-steroidal anti-inflammatory drug (NSAID) diclofenac delivered by NanoEmulsion technology
Indication: Treat osteoarthritis pain
Endpoint: NA
Status: Phase IIa start
Milestone: Start Phase IIa (mid-2007)
In mid-2007, PARS will begin a Phase IIa trial.

**Sinovac Biotech Ltd. (SVA), Beijing, China**
Product: Panflu pandemic influenza vaccine
Business: Infectious
Molecular target: Not applicable
Description: Inactivated vaccine of avian influenza H5N1 strain reassortanted with a human influenza virus strain
Indication: Prevent influenza virus infection
Endpoint: Meet criteria established by EU; safety
Status: Phase II start
Milestone: Start Phase II (06/2007)
Next month, SVA will begin a double-blind, Chinese Phase II trial in 880 healthy volunteers to evaluate 5, 10 and 15 µg of whole viron intravenous Panflu to 5, 10, 15 and 30 µg of split Panflu. The agent was developed with the Chinese Center of Disease Control and Prevention (China CDC).

**Tapestry Pharmaceuticals Inc. (TPPH), Boulder, Colo.**
Product: Oral TPI 287
Business: Cancer
Molecular target: NA
Description: Third-generation taxane
Indication: Treat cancer
Endpoint: NA
Status: Phase Ib/II start
Milestone: Start Phase Ib/II (mid-2007)
This summer, TPPH will begin a Phase Ib/II trial in refractory cancer patients. The trial will evaluate an initial oral dose of TPI 287 followed 1 week later by an intravenous dose of TPI 287 or vice versa, followed by 4 weekly IV doses. The IV formulation is in a Phase II trial for hormone refractory prostate cancer.

Product: TPI 287
Business: Cancer
Molecular target: Not available
Description: Third-generation taxane
Indication: Treat hormone refractory prostate cancer
Endpoint: NA
Status: Phase Ib/II started
Milestone: Start Phase Ib/II (mid-2007)
TPPH began a Phase II trial of intravenous TPI 287.

Indication: Treat glioblastoma multiforme
Endpoint: NA
Status: Phase II start
Milestone: Start Phase II (2H07)
Next half, XNPT will begin a Phase II trial of twice-daily oral XP19986.

**Ziopharm Oncology Inc. (ZIOP), New York, N.Y.**
Product: ZIO-101
Business: Cancer
Molecular target: Not available
Description: Transported prodrug of L-dopa
Indication: Treat Parkinson’s disease (PD)
Endpoint: NA
Status: Phase II start
Milestone: Start Phase II (2H07)
In 4Q07, XNPT will begin a U.S. Phase I trial of oral XP21279.
OFферINGS & SECURITIES TRANSACTIONS

Week ended 5/11/07. Shares after offering refers to shares outstanding. Proceeds are gross, not net. Shares offered don’t include overallotments. Currency rates used in the week: C$=US$0.9029; CHF=$0.8258 €=$1.3597; Rs=$0.02459; SEK=$0.1482

Completed Offerings

**Allon Therapeutics Inc.** (TSX: NPC), Vancouver, B.C.
Business: Neurology, Ophthalmic
Date completed: 5/8/07
Type: Private placement of units
Raised: C$15 million (US$13.5 million)
Units: 12.5 million
Price (unit): C$1.20
Shares after offering: 58.4 million
Note: Each unit consists of a share and half a warrant. Each whole warrant entitles the shareholder to purchase shares at C$1.65 for 2 years.

**Amdl Inc.** (ADL), Tustin, Calif.
Business: Diagnostic
Date completed: 5/4/07
Type: Private placement of common stock and warrants
Raised: $3.8 million
Shares: 12.5 million
Price (unit): C$1.20
Shares after offering: 58.4 million
Note: Each unit consists of a share and half a warrant. Each whole warrant entitles the shareholder to purchase shares at C$1.65 for 2 years.

**Avid Radiopharmaceuticals Inc.** Philadelphia, Penn.
Business: Diagnostic
Date completed: 5/9/07
Type: Venture financing
Raised: $26 million
Investors: AllianceBernstein; SafeGuard Sciences; Pfizer’s Strategic Investment Group; Lilly Ventures; RK Ventures; BioAdvance

**Biodel Inc.** (BIOD), Danbury, Conn.
Business: Drug delivery
Date completed: 5/10/07
Type: IPO
Shares: 5 million
Price: $15
Shares after offering: 19.4 million
Underwriters: Morgan Stanley; Banc of America Securities; Leerink; Natexis Bleichroeder

**Bionvision Inc.** (BIVN), New York, N.Y.
Business: Cancer, Infectious
Date completed: 5/7/07
Type: Warrant exercise
Raised: $6 million
Shares: 3 million
Price: $2
Shares after offering: 59 million
Investor: Perseus-Soros BioPharmaceutical Fund

**CombiMatrix Corp.** (CBMX), Mukilteo, Wash.
Business: Bioinformatics, Microarrays
Date completed: 5/7/07
Type: Private placement of units
Raised: $5 million
Units: 6.8 million
Price (unit): $0.738
Shares outstanding after: 59.6 million
Investors: Company directors; and other investors
Note: Each unit consists of a share and a 5-year warrant to purchase 1.5 shares at $0.55 per share

**Epigenomics AG** (FSE: ECX), Berlin, Germany
Business: Genomics, Diagnostic
Date completed: 5/4/07
Type: Private placement
Raised: €4.9 million ($6.6 million)
Shares: 1.3 million
Price: €3.64
Shares after offering: 18.3 million
Investor: OrbiMed Advisors; Stephens; and other investors

**Immunomedics Inc.** (IMMU), Morris Plains, N.J.

**Zymenex A/S**, Hillerød, Denmark
Product: Metazym
Business: Neurology
Molecular target: NA
Description: Recombinant human arylsulphatase A lysosomal enzyme
Indication: Treat metachromatic leukodystrophy (MLD)
Endpoint: Safety, tolerability, dose-response
Status: Phase I/II started
Milestone: NA
Zymenex began an open-label, Danish Phase I/II trial in 12 patients ages 2-5.

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Completed Offerings, from previous page

**BioCentury Part II**

**May 14, 2007**

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Business: Autoimmune, Cancer, Antibodies
Date completed: 5/7/07
Type: Direct public offering
Raised: $24 million
Shares: 4.8 million
Price: $4.95
Shares after offering: 74.7 million
Placement agent: Janney Montgomery Scott
Investors: Institutional investors

Jevatin Pharmaceuticals Inc. (JAV), Cambridge, Mass.
Business: Neurology
Date completed: 5/10/07
Type: Follow-on
Raised: $42.6 million
Shares: 7.1 million
Price: $6
Shares after offering: 47.9 million
Underwriters: JPMorgan; Pacific Growth; Leerink; Allen; Fortis; Punk
Overallotment: 1.1 million

Karo Bio AB (SSE:KARO), Stockholm, Sweden
Business: Metabolic, Endocrine
Date completed: 5/8/07
Type: Rights offering
Raised: SEK406.4 million ($60.2 million)
Shares: 38.7 million
Price: SEK10.50
Shares after offering: 116.1 million
Advisors: Catella; Mangold
Note: Existing shareholders had the right to purchase 1 new share for every 2 shares held

Kinaxo Biotechnologies GmbH, Martinsried, Germany
Business: Proteomics, Supply/Service
Date completed: 5/7/07
Type: Venture financing
Raised: Not disclosed
Investors: Mountain Partners AG; KfW; High-Tech-Gründerfonds; Max Planck Society; BioM AG and other investors

MorphoSys AG (FSE:MOR), Martinsried, Germany
Business: Antibodies, Dermatology, Cancer
Date completed: 5/3/07
Type: Private placement
Raised: €32.6 million ($44.5 million)
Shares: 652,188
Price: €50
Shares after offering: 7.4 million
Placement agent: Janney Montgomery Scott

Pharmion Corp. (PHRM), Boulder, Colo.
Business: Cancer, Hematology, Cardiovascular
Date completed: 5/10/07
Type: Follow-on
Raised: $120 million
Shares: 4 million
Price: $30
Shares after offering: 36.2 million
Underwriters: Banc of America Securities; Cowen; Pacific Growth; Friedman Billings Ramsey; HSBC
Overallotment: 600,000

Portola Pharmaceuticals Inc., South San Francisco, Calif.
Business: Cardiovascular
Date completed: 5/7/07
Type: Venture financing
Raised: $70 million
Investors: Brookside Capital; AllianceBernstein LP; Teachers Private Capital; Goldman Sachs; T. Rowe Price; IBT Management (IBTM); CDC Consultants Inc; Abingworth Management; Alta Partners; Advanced Technology Ventures; Frazier Healthcare Ventures; MPM Capital; Prospect Venture Partners; Sutter Hill Ventures

Progen Pharmaceuticals Ltd. (ASX:PGL; PGLA), Brisbane, Australia
Business: Cancer
Date completed: 5/9/07
Type: Private placement
Raised: $2 million
Units: 1.3 million
Price (unit): $1.50
Shares after offering: 53.5 million
Placement agent: Thomas Weisel
Investors: Institutional investors

Sidec Technologies AB, Stockholm, Sweden
Business: Proteomics
Date completed: 5/7/07
Type: Venture financing
Raised: SEK68.5 million ($10.2 million)

StrataGent Life Sciences Inc., San Jose, Calif.
Business: Drug delivery
Date completed: 5/10/07
Type: Venture financing
Raised: $6.7 million
Investors: Essex Woodlands Health Ventures; Quantum Technology Partners; Aphelion Capital
Note: The company hopes to raise an additional $9.4 million in the round

ThromboGenics Ltd. (Euronext:THR), Leuven, Belgium
Business: Cardiovascular
Date completed: 5/9/07
Type: Private placement
Raised: €23.9 million ($32.5 million)
Shares: 2.2 million
Price: €10.80
Shares after offering: 25.1 million
Managers: KBC; Kempen

Upstream Biosciences Inc. (UPBS), Vancouver, B.C.
Business: Diagnostic
Date completed: 5/7/07
Type: Private placement of units
Raised: $2 million
Units: 1.3 million
Price (unit): $1.50
Shares after offering: 46.2 million
Note: Each unit consists of a share, a Series A warrant, and a Series B warrant. Each Series A warrant is exercisable at €1.75 and each Series B warrant is exercisable at €1.85 for 2 years.

Proposed Offerings

4SC AG (FSE:VSC), Martinsried, Germany
Business: Autoimmune, Cancer, Computational chemistry/biology
Date announced: 5/10/07
Type: Rights offering
To be raised: €16 million ($21.8 million)
Shares: 5.7 million
Underwriter: Conrad Hinrich Donner

ImaRx Therapeutics Inc. (Proposed:IMRX), Tucson, Ariz.
Business: Cardiovascular, Cancer
Date announced: 5/4/07
Type: IPO
Shares: 3 million
Price: $6.50-$7.50
Shares after offering: 9.1 million
Underwriters: Maxim Group; Jefferies; First Albany
Overallotment: 450,000
Note: ImaRx pulled its original IPO attempt in December, citing market conditions. The company had been seeking to sell 5 million shares at $10-$12 through CIBC World Markets; Jefferies; and First Albany.

Business: Infectious
Date announced: 5/9/07
Type: Private placement of common stock and warrants
To be raised: Up to $35 million
Placement agents: Needham; WBB Securities
Shares outstanding prior: 18.2 million
Price prior: $1.80

Targanta Therapeutics Inc. (Proposed:TARG), Cambridge, Mass.
Business: Infectious
Date announced: 5/11/07
Type: IPO
To be raised: Up to $86.3 million
Shares: TBD
Price: TBD
Underwriters: Credit Suisse; Cowen; Lazard; Leerink
Overallotment: TBD

Amended Offerings

Addex Pharmaceuticals S.A., Geneva, Switzerland
Business: Neurology
Date announced: 5/9/07
Type: IPO

See next page
Amended Offerings, from previous page

To be raised: CHF135 million ($111.5 million)
Shares: 1.8-2.3 million
Price: CHF58-CHF75
Underwriters: Lehman; Piper Jaffray; Vontobel; Bank am Bellevue
Overallotment: 349,138
Note: Addex plans to list on the SWX Swiss Exchange

Endoceutics Inc. (Proposed: ENCX), Quebec, Quebec
Business: Cancer, Endocrine
Date announced: 5/9/07
Type: IPO
Shares: 5.4 million
Price: $13-$15
Underwriters: UBS; JPMorgan; Leerink, Pacific Growth
Overallotment: 810,000
Note: In February, Helicos filed to raise up to $100 million

Other Financial News

Conatus Pharmaceuticals Inc., San Diego, Calif.
Business: Inflammation, Infectious, Metabolic
Date announced: 5/9/07
Conatus raised $22 million in a second close of its series A round, bringing the total raised in the round to $27.5 million. The company’s existing investors participated in the second close. Conatus raised $5.5 million in a first close on Jan. 3.

Emergent Technologies Inc., Austin, Texas
Business: Finance
Date announced: 5/7/07
Emergent Technologies closed its $27.1 million fund, Emergent Technologies Fund IV. The fund will be used to develop biotechnology applications derived from the University of Texas.

Gilead Sciences Inc. (GILD), Foster City, Calif.
Business: Biopharmaceuticals, Infectious, Pulmonary
Date announced: 5/8/07
GILD’s board approved a 2-for-1 stock split. The company’s shares will begin trading on a split-adjusted basis on June 25. GILD will have 931.1 million shares outstanding post split.

Nextech Venture, Zurich, Switzerland
Business: Finance
Date announced: 5/7/07
Nextech is raising a new venture capital fund dedicated to companies developing cancer therapeutics. The fund, which had an initial close of €25 million ($35 million), will invest in companies with products in late preclinical and/or early clinical development.

Oragenics Inc. (ONI), Alachua, Fla.
Business: Dental
Date announced: 5/7/07
ONI received a letter from AMEX saying the company is not in compliance with certain listing standards

Pluristem Life Systems Inc. (PLRS), Haifa, Israel
Business: Gene/Cell therapy
Date announced: 5/9/07
The company listed on the Frankfurt Stock Exchange under the symbol “PJT.” The company will continue to list on the OTC Bulletin Board.

Shire Pharmaceuticals Group plc (LSE:SHP; SHPGY), Basingstoke, U.K.
Business: Neurology, Gastrointestinal, Metabolic
Date announced: 5/8/07
SHP raised $100 million to cover overallotments from its May 2 convertible bond financing, bringing the total raised to $1.1 billion. The bonds bear 2.75% interest and mature in 2014.