End the war

The firestorm over GlaxoSmithKline plc’s Avandia rosiglitazone, which was rekindled two weeks ago with an incendiary Senate report, shows why people who live outside the Beltway are convinced that Washington is broken, and why they are right.

The politico-media outburst exemplifies the worst aspects of the American regulatory environment.

It also exemplifies why business as usual in Washington must stop, and why the responsibility rests directly at the feet of the politicians and regulators who are failing their responsibility to put the public’s health before politics.

As with previous rounds in the Avandia circus, grandstanding members of Congress played gotcha with FDA, releasing their report to the agency and to the media simultaneously. The sneak attack by the Senate Finance Committee once again accused the agency and GSK of ignoring serious cardiovascular risks during years of patient access to Avandia to treat Type II diabetes.

Citing data from disgruntled FDA employees, Committee Chair Max Baucus (D-Mont.) and ranking member Chuck Grassley (R-Iowa) said in a Feb. 20 press release that “the FDA itself estimated that the drug caused approximately 83,000

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excess heart attacks between 1999 and 2007.” The release gave the false impression that this represents FDA’s official position.

The timing preempted FDA’s plans to announce an advisory committee meeting in July to review all of the safety data on Avandia, especially the agency’s detailed analysis of the RECORD study, which is the only prospectively designed cardiovascular outcomes trial of the drug.

Unless the political leadership at HHS and FDA acts quickly and decisively, decision-making based on external political pressure and a paralyzing precautionary philosophy will become institutionalized. Instead of being occasionally blown off course by recurring squalls, the very real risk is that permanent climate change will forever degrade FDA’s science-based oversight process, eroding the public’s confidence in the agency and placing a stop sign on the path of biomedical innovation.

Avandia is the poster child for a culture that has evolved at FDA — encouraged by publicity-seeking politicians — in which agency employees who dislike a regulatory decision are able to keep raising the issue, and if they don’t like the results, to go outside established agency procedures for resolving scientific disputes to enlist support from members of Congress and their enabling lapdogs in the media.

The tactic consists of asking the same question over and over, while impugning the morality and motives of anyone who disagrees, until dissenters get the decisions they want.

This creates a poisonous atmosphere at FDA. Senior managers know any decision can be appealed to Congress, which at a minimum means that they will have to spend hundreds or thousands of hours responding to inquiries and documenting their actions.

In the Avandia case, this diversion of focus cannot be good news for patients who hope ultimately to benefit from the over 400 active INDs under the oversight of CDER’s Metabolic and Endocrine Division.

These are the same patients who are being told yet again by politicians that FDA and their physicians have failed them.

Ambulance-chasers in and out of government have certainly gotten the message. Santa Clara County in Northern California, in the midst of the world’s largest biotech cluster, has hired three tort lawyers on a contingency basis to sue GSK over Avandia.

The complaint is peppered with quotes from the Finance Committee report.

In a Washington defined by instant communications, silence signals agreement or guilt. And so far, it doesn’t look like FDA Commissioner Margaret Hamburg or HHS Secretary Kathleen Sebelius are rising to the challenge.

Last week, Hamburg missed a March 4 deadline Baucus and Grassley set for responding to accusations raised in their report.

Indeed, Hamburg and Sebelius have been almost silent for over two weeks after members of Congress, influential physicians like Steven Nissen, chairman of the department of cardiovascular medicine at the Cleveland Clinic, and pundits charged in newspapers, television and the Internet that the agency’s corruption, negligence and complacency has led to thousands of needless deaths.

Meanwhile, the FDA staff whose decisions are being second-guessed have been muzzled.

**Something from nothing**

A rational person might have trouble taking seriously the threat from the Senate Finance Committee and the resulting publicity because there are no new scientific or medical data on the table.

The first Avandia safety circus started in May 2007, when members of Congress collaborated with Nissen and the New England Journal of Medicine to co-opt FDA’s planned release of a safety advisory about use of the PPAR gamma agonist to improve glycemic control in adults with Type II diabetes (see BioCentury, May 28, 2007).

The Finance Committee used the same playbook this time around, timing the Feb. 20 release of its report to preempt FDA’s plans to announce the July advisory committee meeting to review the accumulated safety data, especially from RECORD.

The strategy worked perfectly: FDA was caught flat-footed and its announcement of an advisory committee meeting now looks like a response to political pressure, rather than an outcome of its data-based internal deliberations.

When the Finance Committee gave FDA a copy of its report on Avandia on Friday, Feb. 19, it had already leaked a copy to The New York Times, allowing the newspaper to report the committee’s allegations on Saturday, a day before the report was released to the public.

The report’s main messages were that GSK had pulled the wool over FDA’s eyes about Avandia’s CV safety, hiding blatant safety risks for years, while FDA refused to act even after righteous researchers revealed the company’s perfidy.

In their press release, Baucus and Grassley charged that “FDA has been too cozy with drug makers and has been regularly outmaneuvered by companies that have a financial interest in downplaying or under-exploring potential safety risks.”

They also said “FDA has overlooked or overridden safety concerns cited by its own officials.”

The press release said Finance Committee staff had spent two years working on the 342-page report and reviewed over 250,000 pages of documents.

Despite all this effort, the staff failed to note some of the most salient data about Avandia. There isn’t a word about the final results of RECORD, which in fact demonstrated a cardiovascular safety profile in line with FDA’s requirements for diabetes treatments (see BioCentury, June 8, 2009).

Instead, the report characterizes RECORD as simply a “marketing tool for competition.”

The Senate report dwells on the study’s known weaknesses — patients in the trial experienced far fewer cardiac events than had been anticipated, limiting its statistical power — but nothing is said about the deep skepticism that FDA and most physicians have about the definitiveness of meta-analyses of short studies that weren’t designed to be pooled, which were, and continue to be, at the heart of the attack on the drug.

Last Monday, Rep. Rosa DeLauro (D-Conn.) issued a statement urging FDA to withdraw Avandia from the market “until a truly independent, science-based advisory panel can evaluate the safety and effectiveness of the drug.”

Perhaps because it also was not mentioned in the Finance Committee report, DeLauro conceivably could have been unaware of an August 2007 FDA advisory
committee’s 22-1 vote recommending that Avandia remain on the market (see BioCentury, Aug. 6, 2007).

Perhaps she is ignoring that inconvenient truth. Either way, DeLauro has no excuse. She chairs the House subcommittee that authorizes FDA’s budget.

That responsibility did not stop DeLauro from concluding a day after the Finance Committee issued its report that “the Avandia case provides further evidence that patients should not trust drug companies with their health.”

DeLauro will have an opportunity to discuss the data with Hamburg on Wednesday this week when the House holds FDA budget hearings.

Old news

Although there was no new information in the Senate report, it generated a flood of press coverage suited to these kinds of politically inspired witch hunts. Virtually all the coverage accused FDA of negligence or complicity in the unnecessary deaths of thousands of Americans.

No one from FDA or HHS publicly refuted the allegations.

When someone as powerful as Baucus releases a one-sided report that ignores pertinent evidence, imperils patients by scaring them into abandoning medicines that FDA and its outside experts have deemed effective, and accuses FDA of complicity in thousands of needless deaths and heart attacks, Sebelius or Hamburg have an obligation to call them to account.

Instead, FDA and HHS have done nothing to defend their staff against accusations of misconduct. Indeed, FDA decided not to allow any media interviews about Avandia, agency spokesperson Karen Riley told BioCentury a few days after the report was released.

A three-line statement and a bland “Safety Communication” were the only official responses to the 342-page Finance Committee report and thousands of newspaper articles and television broadcasts disseminating attacks on the agency’s handling of Avandia.

A Feb. 27 editorial in the Norfolk Virginian-Pilot, titled “FDA’s failures are killing us,” is typical of the media response. Using data provided to the Finance Committee by whistleblower David Graham of FDA’s Office of Surveillance and Epidemiology (OSE), the newspaper concludes that “by the agency’s own estimates, Avandia caused 83,000 heart attacks between 1999 and 2007.”

In its meager statement, FDA said it “takes very seriously concerns and issues raised in the recent inquiry from Senators Baucus and Grassley. CDER Center Director Janet Woodcock issued a memo in December 2009 requesting that all appropriate offices within the Center rapidly evaluate the new data with the aim of presenting it to an FDA Advisory Committee in the summer of 2010. FDA awaits the recommendations of the advisory committee, and in the meantime Dr. Hamburg plans to meet with FDA scientists and outside experts to gain a full understanding and awareness of all of the data and issues involved.”

Woodcock was permitted to conduct a telephone briefing on Feb. 22 for key medical opinion leaders.

On the call, which was not disclosed to the media, Woodcock said “FDA is in possession of no new data that raises alarms” about Avandia’s safety. She noted the agency’s 2007 decision to allow Avandia to remain on the market with a boxed warning about CV risk and said “we don’t find the available information since that time has changed the assessment.”

Woodcock noted that FDA hasn’t learned anything since 2007 to prompt it to reverse its 2007 decision to keep Avandia on the market. She told Zachary Bloomgarden, a clinical professor at Mount Sinai Medical Center: “There is no startling source of definitive information that immediately hits you in the face and tells you this is the answer.”

Prominent cardiologists have come to a similar conclusion. A few days after the Finance Committee report was released, the American Heart Association and American College of Cardiology Foundation issued a scientific advisory stating that the two FDA-approved thiazolidinediones, Avandia and Actos pioglitazone from Takeda Pharmaceutical Co. Ltd., are appropriate second-line diabetes therapies.

AHA and ACC pointedly note that “insufficient data exist to support the choice of pioglitazone over rosiglitazone.”

The scientific statement emphasized the need for a head-to-head study comparing Actos to Avandia.

This would run counter to the one bit of news in the Finance Committee report. It reveals that Graham, who is associate director for science and medicine at OSE, and another FDA safety officer circulated a memo in October 2008 reiterating their call for withdrawal of Avandia. In it, they argued that the FDA-mandated Phase IV TIDE trial comparing Avandia to Actos was “unethical and exploitative.”

If Graham were now allowed to talk publicly, he should be asked about whether his ethical views extend to another FDA-mandated Phase IV CV outcomes trial, the PRECISION trial comparing Celebrex celecoxib from Pfizer Inc. to ibuprofen or naproxen. Like Avandia, Graham has publicly stated that Celebrex is so dangerous that it should be withdrawn.

The fact is EMA won’t allow European patients to enroll in PRECISION because the regulators have concluded it would be unethical. Graham’s silence on this may have something to do with the fact that Nissen, the primary investigator on PRECISION, is one of his allies in the battle against Avandia.

Meanwhile, among its other omissions, the Finance Committee does not note that numerous U.S. IRBs, as well as equivalent bodies in 16 other countries, have determined that TIDE is ethical and safe.

Perhaps that, too, is simply an oversight. But the TIDE trial could be exculpatory, as it is designed to test the CV effects of long-term treatment with Avandia or Actos when used as part of standard of care compared to similar standard of care without either drug in patients with Type II diabetes who have a history of or are at risk for CV disease.

On FDA’s clinician call, Woodcock told another endocrinologist that “our position is we are still quite uncertain about the myocardial ischemic risk of Avandia based on the data we have.” She noted the RECORD investigators’ conclusions that the trial demonstrated non-inferiority on CV safety compared to standard of care diabetes drugs and said “we are neither accepting nor rejecting that conclusion.”

Woodcock said FDA is reviewing the RECORD data, which it received last summer, “with a fine-tooth comb” in advance of the July advisory committee meeting.
Siege guns

The critical issue is not what FDA ultimately decides to do about Avandia, but how it makes the decision. In this regard, the composition of the advisory committee and the quality of the data presented will be critical.

Graham is almost certain to play a major role in the meeting. He has led a crusade against Avandia and other drugs, and already has testified to Congress that FDA puts industry interests ahead of the public’s health — indeed, charging the agency has “lied” to Congress and the American public in its effort to protect the industry.

At the 2007 meeting, Graham presented data from an observational study that he had first shown to FDA management only days before the meeting. Committee members sharply criticized the agency for asking them to consider data that had not been peer reviewed or independently vetted. It will be interesting to see if Graham repeats the tactic in July.

It is a safe bet, however, that FDA’s internal critics, as well as academic physicians who favor creating an independent safety center at FDA, won’t wait for the July meeting or accept its results if it doesn’t recommend immediate withdrawal of Avandia.

They’ll be citing the Finance Committee report as evidence of the need to reform FDA in the pages of medical journals, in the national media, and in public meetings about reauthorization of PDUFA.

Meanwhile, GSK will be defending Avandia in the courts long after Avandia’s 2012 patent expiration.

Lawyers seeking to cash in on the Avandia scare have been recruiting clients for years, and were quick to put links to the Finance Committee report on their websites within hours of its release.

Santa Clara County also mentioned the Senate report prominently in its Feb. 26 civil suit accusing GSK of falsely advertising Avandia.

Santa Clara County includes Silicon Valley, which is ground zero for venture capital, home to numerous biotech companies and is represented in Washington by four Democrats, including biosimilars champion Anna Eshoo.

The county asserts GSK knew Avandia was too dangerous to allow on the market before it filed an NDA, and it seeks restitution for anyone in the entire state of California who ever had a heart attack while taking Avandia.

That GSK’s labeling was approved — mandated, in fact — by FDA is irrelevant, as is the advisory committee’s decision that the drug should remain on the market, Tamara Lange, lead deputy county counsel for Santa Clara, told BioCentury last week.

“The case is focused on the conduct of GSK, on the false and misleading statements it made in advertising,” she said. “GSK may contend it was simply following FDA’s instructions, but I don’t think there is much merit” to that claim.

The status quo

The Finance Committee’s release also undoubtedly was timed to influence the upcoming PDUFA negotiations and build a case for separating drug safety oversight from new drug reviews. Even though Congress rejected that idea during the first Avandia blowup, the vigor of the new populist broadside suggests FDA may be approaching a tipping point.

As BioCentury has already reported, the biotech industry is debating whether it should use PDUFA reauthorization negotiations to seek changes at FDA that could make drug registration more predictable and less time-consuming, or if it should adopt a minimalist approach that will maintain the status quo (see BioCentury, Feb. 15).

The problem is that Avandia is the status quo. And while the industry is fiddling, self-styled consumer advocates who would separate safety and efficacy — a policy that would ultimately deny patients access to drugs — have made use of their ready access to top FDA officers and undoubtedly are using these opportunities to frame the debate.

Two drug industry critics who favor this policy, former New England Journal of Medicine Editor Marcia Angell, and Public Citizen’s Sidney Wolfe, visited with FDA Principal Deputy Commissioner Joshua Sharfstein at the end of January.

Sharfstein may tip some of his views about Avandia on Wednesday this week when he appears before a House Energy and Commerce health subcommittee hearing on drug safety.

Drug developers, and the patients who rely on them to create new cures, have no choice but to come out fighting for what’s right. But at the end of the day, the current mess is a government creation, and only the political classes can change it.

Until then, the “it’s never over” culture in Washington is destroying the predictability of the regulatory process that enables drug developers to take on the risk of creating new medicines.

As a result, it will deprive American patients and their caregivers of the new treatments that they have the right to expect from new science, done carefully, thoroughly and prudently.

What is left over is the truth about power. In this case, it’s about who gets to decide if a drug is approved or withdrawn, and whether those decisions will be based on dispassionate scientific and medical judgment that balance benefit and risk, or whether they will be made based on populist demagoguery, orchestrated media campaigns and personal rivalries among FDA staff.

In their years out of power, Democrats spent a great deal of time ridiculing Republicans for their lack of respect for science. Now that they control all three branches of government, they need to show that these were not just empty words.

COMPANIES AND INSTITUTIONS MENTIONED

American Heart Association, Alexandria, Va.
American College of Cardiology, Washington, D.C.
Cleveland Clinic, Cleveland, Ohio
European Medicines Agency (EMA), London, U.K.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK) London, U.K.
Mount Sinai Medical Center, New York, N.Y.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
U.S. Food and Drug Administration (FDA), Silver Spring, Md.
Merck’s chemical test

By Mike Ward
Senior Editor

Merck KGaA has put its own spin on the trend among mid-size European companies to choose between their prescription drugs and chemical businesses. Last week the company confirmed its commitment to a dual business strategy by unveiling plans to buy U.S. laboratory and biotech supply company Millipore Corp. for €7.2 billion.

By enhancing its performance chemicals business, Merck hopes to catalyze growth. Last month, the pharma said it expects overall group growth this year of 3-7%. Revenues from Merck Serono S.A., which account for 70% of the company’s drugs business, are predicted to grow only 2-5% in 2010.

In contrast, its consumer healthcare products are forecast to grow 5-10%, liquid crystal display (LCD) chemicals revenues are expected to advance by a similar amount, and performance and life science chemicals sales were guided to increase 3-8%.

More importantly, the operating margins on Merck’s chemical operations are superior to those of the pharma business. So the company is moving even further into the chemicals space.

Other European mid-caps that once ran chemical businesses, such as Akzo Nobel N.V., Solvay S.A. and UCB Group, have opted to focus on one business and divest the other.

UCB started the trend in 2004 when it sold off its chemicals business and acquired Celltech Group plc, at the time Europe’s largest entrepreneurial biotech company. In 2006, UCB added Schwarz Pharma AG to its family. In 2007, Akzo Nobel divested its pharmaceuticals and animal health arm when it sold its Organon BioSciences N.V. subsidiary to Schering-Plough Corp., now part of Merck KGaA.

In 2009, Merck KGaA announced its intention to merge Millipore with its laboratory chemicals business, which provides raw materials for pharmaceutical and biotechnology products, to create a new life sciences and process solutions division. The resulting business, to be called Merck Millipore, would have an annualized growth, while operating profit has grown 18.1% per annum.

Operating profit of $341 million, with an operating margin of 12.5X EBITDA if the anticipated annual savings of $100 million are factored in.

““These are not commodity chemical businesses, and pharmaceuticals do not always have high margins.””

Karl-Ludwig Kley, Merck KGaA

“Late last year, FDA refused to file an NDA for cladribine, an oral purine nucleoside analog that inhibits DNA synthesis, to treat relapsing forms of MS. Merck licensed cladribine from Teva Pharmaceutical Industries Ltd. Moreover, European Medicine Agency’s CHMP recommended against extending the indication for Merck’s Erbitux cetuximab to include first-line treatment of patients with EGFR-expressing, advanced or metastatic non-small cell lung cancer (NSCLC) in combination with platinum-based chemotherapy (see BioCentury, Dec. 7, 2009).”

Now, Merck wants to rebalance its revenues. Last year, pharmaceuticals accounted for 75% of the group’s revenues and chemicals for 25%.

“Our strategy is to spread entrepreneurial risk by being involved in both pharmaceuticals and chemicals. This served us very well last year when LCD chemicals took a hard hit, while the pharma business was relatively steady,” spokesman Phyllis Carter told BioCentury.

Merck’s $107 per share bid for Millipore was a 13% premium over the previous week’s closing price of $94.41, and 50% above the Feb. 19 share price when rumors of a potential bid began to circulate.

Merck is paying 15.1X Millipore’s estimated 2010 EBITDA, or 12.5X EBITDA if the anticipated annual savings of $100 million are factored in.

“This transaction is fully in line with our acquisition strategy in that it focuses on high-margin specialty products with an attractive growth profile, cutting-edge technology in life sciences and expands geographical reach, especially into the U.S.,” Merck Chairman Karl-Ludwig Kley said on a conference call.

“We have always been very clear that [performance chemicals] is a sustainable, long-term part of our business model. It’s about risk diversification rather than synergies,” he added.

“These are not commodity chemical businesses, and pharmaceuticals do not always have high margins.”

Millipore has two units: the bioscience division makes products used in life science R&D; the bioprocess division makes biologics do not always have high margins.”

Merck intends to merge Millipore with its laboratory chemicals business and the majority of its life science reagents and chemicals solutions activity, which provides raw materials for pharma production. Together, these generated revenues of €900 million ($1.2 billion) in 2009. The pro forma revenues of the resulting business, to be called Merck Millipore, would have
been €2.1 billion.

Following the merger, Merck’s chemicals business will be responsible for 35% of the group’s revenue, up from 25% (see “Merck Plus Millipore”).

The fastest-growing segment of Merck Millipore is expected to be the bioscience research segment, which is forecast to grow 6-10% annually. In 2009, Millipore sales for this segment were €310 million ($421 million), compared with Merck’s €77 million ($105 million).

Sales of high quality chemicals and technologies to industrial and academic labs is forecast to grow 2-6%, with Merck providing €453 million and Millipore €214 million.

Bioprocessing sales are anticipated to rise 4.8% in 2010. In 2009, Millipore sales to this segment were €667 million, while Merck posted €345 million.

The merger will also triple Merck’s life sciences chemicals sales in the U.S. from €262 million to €737 million, while revenues in the European and Asian markets will more than double.

On the product development side, Merck Millipore’s pro forma 2009 R&D budget at €123 million would have placed it third in the market behind Life Technologies Corp., which spent €240 million in 2009, and Thermo Fisher Scientific Inc., which invested €177 million in R&D last year.

Reckmann estimated that on a pro forma basis, the combined company would have had 2009 revenues of €8.9 billion, EBITDA of €2 billion, an operating margin of 23% and EPS of €4.87, 10% over Merck’s solo performance.

The Millipore acquisition will be funded through available cash and a term loan provided by Bank of America Merrill Lynch, BNP Paribas and Commerzbank AG. Merck said it plans to replace part of the facility through the issuance of bonds.

COMANIES AND INSTITUTIONS MENTIONED

Abbott Laboratories (NYSE-ABT), Abbott Park, Ill.
Akebia (Xeta:MRK), Darmstadt, Germany
Akzo Nobel N.V. (Euronext:AKZ; AKZOY), Arnhem, the Netherlands
Alcon (Xetra:BAY), Leverkusen, Germany
Bayer AG (Xetra:BAY), Leverkusen, Germany
Bayer (Xetra:MRK), Darmstadt, Germany
Millipore Corp. (NYSE:MIL), Billerica, Mass.
Mylan Inc. (NASDAQ:MYL), Canonsburg, Pa.
Solvay S.A. (Euronext:SOLOB), Brussels, Belgium
Teva Pharmaceutical Industries Ltd. (NASDAQ:TEVA), Petah Tikva, Israel
UCB Group (Euronext:UCB), Brussels, Belgium

Merck KGaA (Xetra:MRK), Whitehouse Station, N.J.
Millipore Corp. (NYSE:MIL), Billerica, Mass.
UCB Group (Euronext:UCB), Brussels, Belgium

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March 8, 2010

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Acorda (NASDAQ:ACOR) B6
Actelion (SIX:ATLN) A7, B12
Adams (OTCBB:ADMP) B2
Advanced Cell Tech (OTCBB:ACTC) B9
AventRx (NYSE-A:ANX) B9
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Ariad (NASDAQ:ARIA) B10
ArQule (NASDAQ:ARQL) B19
Astellas (Tokyo:4503) A9, A23, B5, B7
AstraZeneca (LSE:AZN; NYSE:AZN) B3, B7
AzErx B19
Banyu B18
B&L A21, B4

Baxter (NYSE:BAX) A5, A20, B2
Bayer (NYSE:BAY) A7, A10, B10
Biodel (NASDAQ:BODI) A21, B10
BioDelivery (NASDAQ:BDSI) B13
Biogen Idec (NASDAQ:BIIB) B9, B10
Bioject (OTCBB:BCT) B20
BioMarker Group B6
BioMS A22
Bionomics (ASX:BNO; OTCBB:BMICY) B14
BioSante (NASDAQ:BPA) A21, B22

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Actelion hasn’t seen top of PAH

By Stephen Hansen
Staff Writer

Actelion bosentan’s failure in idiopathic pulmonary fibrosis likely marks the end of potential label expansions for the drug. But Actelion Ltd., believes it can still grow the product’s sales through geographical and patient expansion in its core indication of pulmonary arterial hypertension.

The company also has two more PAH candidates in Phase III testing — including a more potent follow-on to Tracleer that might succeed in IPF — as well as two Phase III compounds in other indications.

Tracleer posted CHF1.5 billion ($1.5 billion) in worldwide sales in 2009, accounting for 89% of Actelion’s CHF1.7 billion ($1.6 billion) in product revenue. Although the company does not break out Tracleer sales by region, total product revenue included CHF763.5 million in the U.S., up 24% from the prior year, and CHF702.4 million in Europe, an 11% gain.

For the rest of the world (ROW), sales were CHF232.1 million, up 29% vs. the prior year.

Actelion also does not provide specific guidance for Tracleer. In February, the biotech said it expects 2010 total revenue growth to be above 10% in local currencies.

Last week, Tracleer missed the primary endpoint of significantly reducing time to occurrence of disease worsening or death vs. placebo (p=0.21) in the double-blind, international Phase III BUILD-3 trial in 616 patients with IPF.

No further trials of Tracleer will be conducted in IPF, which was the last of several label expansions the company had hoped for. Tracleer was first approved for WHO Class III-IV PAH in the U.S. in November 2001 and in Europe in May 2002. WHO Class II PAH, a milder form of the disease, was added to both labels last year. Also last year, a pediatric formulation of Tracleer for PAH was approved in the EU.

In 2007, Tracleer was approved in the EU to reduce the number of new digital ulcers in patients with systemic sclerosis. The company abandoned its plans to add the indication to the U.S. label because FDA wanted a clinical trial for healing and treatment of digital ulcers, rather than a prevention label.

Actelion could try again if a preventive label were deemed acceptable in the future, according to spokesperson Roland Haefeli.

Actelion has been unsuccessfully tested in metastatic melanoma, sickle cell disease associated with pulmonary hypertension and chronic thromboembolic pulmonary hypertension (CTEPH).

The only remaining company-sponsored study is the Phase III COMPASS-2 trial of Tracleer plus Revatio sildenafil to treat PAH. The company does not know when to expect data from the event-driven trial. Investigator-sponsored trials of Tracleer are ongoing in other indications such as sarcoidosis, poorly controlled asthma and diabetic nephropathy.

Despite Actelion’s limited options for expanding Tracleer’s label, CEO Jean-Paul Clozel told BioCentury he believes the company can continue to grow the product’s sales for approved indications through geographical and patient expansion.

“The PAH market is still by far not filled. Many patients are not diagnosed,” Clozel said. “And we are also launching, and going to launch in many countries, where Tracleer was not launched before.”

According to Haefeli, only 20-30% of patients who have PAH are correctly diagnosed, so there is room to expand the population by continuing to support improved diagnosis and treatment of the condition.

The company already does this through its PAH patient registries, medical science specialists and educational seminars and meetings with patients and physicians. Haefeli also said Actelion’s support of academic researchers in PAH, combined with its own research, leads to a dissemination of PAH information, which increases disease awareness.

On the geographical front, Actelion reacquired Nordic rights to Tracleer from Swedish Orphan International AB last December after that company was acquired by Biovitrum AB (now Swedish Orphan Biovitrum). Sales figures for Tracleer in the region are not disclosed.

Actelion is accelerating marketing of Tracleer in regions where it is already approved, such as China, Japan, Mexico, Brazil and Turkey. For example, the company is expanding its field force in China, and doubling its sales force in Japan.

The company also has yet to launch in several countries where Tracleer is approved, including Russia, Chile, Peru, the Middle East and north Africa.

While these markets are small in comparison to the major markets, “they do add up and provide a sizeable contribution to product sales,” said Haefeli.

In 2009, ROW revenues accounted for 14% of Actelion’s total product revenues.

Clozel also noted that Actelion will be expanding its PAH franchise in the next few months through the launch of intravenous epoprostenol, which was approved for PAH in the U.S. in June 2008. Actelion acquired the prostacyclin analog from GeneraMedix Inc. last year.

Actelion also markets Ventavis iloprost in the U.S. to treat WHO Class III-IV PAH. Bayer AG markets the inhaled prostacyclin analog elsewhere.

Outside of PAH, Actelion is looking to expand sales of Zavesca miglustat. The oral N-butyldeoxynojirimycin glucosyltransferase inhibitor is approved in the U.S. and EU to treat patients with Type I Gaucher’s disease for whom enzyme replacement therapy (ERT) is unsuitable. The company expects data this year from the Phase III MAINTENANCE trial of Zavesca as maintenance therapy in Gaucher’s patients who have switched from ERT.

Zavesca is also marketed in the EU to treat progressive neurological manifestations in patients with Niemann-Pick type C disease and under review in the U.S. for the indication, with a March 10 PDUFA date.

“The PAH market is still by far not filled.”

Jean-Paul Clozel, Actelion
Strategy, from previous page

In the pipe

Actelion also has four compounds in Phase III testing, two of which are in development for PAH: macitentan and selexipag. The first of these is intended to replace Tracleer, which begins to lose patent protection in major markets at the end of 2015.

Macitentan is a tissue-targeting endothelin receptor antagonist with more potent target inhibition than Tracleer. Data from the Phase III SERAPHIN trial in PAH are expected in 2012.

As it did with Tracleer, Actelion also is likely to pursue additional indications for macitentan. Clozel said the company believes that the trend toward efficacy for Tracleer in the BUILD-3 trial may indicate that a more comprehensive blockade of endothelin receptors is necessary to show an anti-fibrotic effect in IPF.

He noted macitentan is up to 100 times more potent at blocking the endothelin A and endothelin B receptors than Tracleer. “We know that macitentan is a much more powerful endothelin receptor antagonist than Tracleer, and you can go to higher doses without hitting side effects than you can with Tracleer,” Clozel added. “Because of that and our preclinical experiments, we believe that we have a good chance to see a larger effect.”

Actelion expects to complete enrollment of the Phase II MUSIC trial of macitentan in 150 IPF patients this year, with data expected in 2H11. The primary endpoint is improvement in forced vital capacity (FVC) vs. placebo, with a secondary endpoint of reduction in the time to disease worsening or death.

Clozel said he would want to see a very clear trend in favor of macitentan before moving the compound into a long Phase III trial looking at morbidity and mortality.

Hafeli said it is too early to quantify what might be considered a clear trend, because the macitentan data would be compared to the Tracleer BUILD-3 data, which are not yet fully analyzed.

Actelion’s other PAH compound is selexipag, an oral long-acting prostacyclin receptor (PG12) agonist that entered the GRIPHON trial last year. Actelion has existing Japan rights to a 2008 deal with Nippon Shinyaku Co. Ltd.

Because selexipag and epoprostenol target the prostacyclin pathway, Hafeli said it’s possible they could be given in combination with Tracleer or macitentan to hit multiple disease mechanisms.

Clozel said the company’s other Phase III compounds are expected to help drive Actelion’s long-term growth outside its core PAH business.

Data from the Phase III CONSCIOUS-2 trial of Pivlaz clazosentan to prevent the occurrence of cerebral vasospasm following aneurismal subarachnoid hemorrhage (aSAH) are expected in 2H10.

The intravenous endothelin receptor antagonist also is in the Phase III CONSCIOUS-3 trial in patients with aSAH treated by endovascular coiling. Data are expected in 2011.

Actelion’s fourth Phase III compound is almorexant, an antagonist of orexin 1 and 2 receptors (OX1R and OX2R) that has completed one Phase III trial for primary insomnia. The company plans additional Phase III trials, but hasn’t provided a timeline for when they might start.

GlaxoSmithKline plc has worldwide rights to co-develop and co-commercialize almorexant outside Japan. The pharma is responsible for marketing almorexant in emerging markets, and the partners will co-market and equally share profits elsewhere.

Revatio is marketed by Pfizer Inc. to treat PAH and as Viagra to treat erectile dysfunction (ED).

COMPANIES AND INSTITUTIONS MENTIONED

Actelion Ltd. (SIX:ATLN), Allschwil, Switzerland
Bayer AG (Xetra:BAY), Leverkusen, Germany
GeneraMedix Inc., Liberty Corner, N.J.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Nippon Shinyaku Co. Ltd. (Tokyo:4516; Osaka:4516), Kyoto, Japan
Pfizer Inc. (NYSE:PFJE), New York, N.Y.
Swedish Orphan Biovitrum (SSE:BVT), Stockholm, Sweden

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**Strategy**

**OSI’s last stand**

By Aaron Bouchie  
Senior Writer

OSI Pharmaceuticals Inc. has made two strategic decisions in the last five years that investors didn’t like. As a result, it would not be surprising if they refuse to back the company’s independence following last week’s hostile bid by Astellas Pharma Inc. to buy the company for $52 a share, or $3.5 billion.

The problem for OSI is that it has failed in its efforts to buy near-term revenues and it has no near-term drivers from its internal pipeline. Indeed, according to SEC documents released last week by Astellas, during talks between the two companies in 2009, OSI CEO Colin Goddard said “he believed OSI would realize its intrinsic value within two years.”

Given the right price, investors are unlikely to see any reason to wait. Thus the two remaining questions are how much Astellas will have to increase the offer to get the deal done, and whether OSI partner Roche will play the white knight.

**Macugen debacle**

OSI has tried to buy pipeline at least three times in the past decade. In 2001, the company bought Gilead Science Inc.’s cancer portfolio for $130 million in cash and $43 million in stock. OSI received three compounds in development for solid tumors: OSI-211 was a liposomal lurtotecan topoisomerase I inhibitor in Phase II trials; OSI-7836 was a nucleoside analog in Phase I testing; and OSI-7904L was a liposomal thymidylate synthase inhibitor in preclinical development.

In 2004, OSI stopped development of OSI-7836 because of toxicity issues and OSI-211 because it was unable to differentiate the compound from topotecan. The company stopped development of OSI-7904L in 2005.

The next move was a small deal in 2003: $31 million in stock for Cell Pathways Inc. The company had two compounds in mid- and late stage development: Aptsyn exisulind was in Phase III trials to treat non-small cell lung cancer (NSCLC) and CP461 was in Phase II trials to treat several cancer and non-cancer indications (see BioCentury, Feb. 17, 2003).

Aptsyn failed to show improved survival in 2004. OSI dropped development that year and dropped CP461 in 2005. Most important for investors’ views of the company was the decision in August 2005 to buy Eyetech Pharmaceuticals Inc. for $685 million in cash plus $144.7 million in stock. The deal was driven by Eyetech’s Macugen pegaptanib, a pegylated oligonucleotide aptamer that binds to vascular endothelial growth factor (VEGF) to treat age-related macular degeneration (AMD).

Buyers were infuriated, as they believed that OSI was buying a product whose days were numbered. Macugen was approved in December 2004, but its sales were already being eroded by off-label use of Genentech Inc.’s Avastin bevacizumab and investors believed the AMD market would be dominated by the latter’s Lucentis ranibizumab once that was approved, which occurred in July 2006.

Investors also argued the deal was lowering OSI’s growth trajectory from the 20% range into the mid-teens.

And, buyers interpreted the fact that OSI paid mostly cash for the deal as a way to skirt a shareholder vote (see BioCentury, Aug. 29, 2005).

The investor view of Macugen proved correct. OSI recorded $103 million in U.S. sales in 2006 — far below the $350-$370 million that the biotech had expected and well below the analyst consensus estimate of $298.5 million.

As a result, OSI exited the eye business only a year after it completed the Eyetech acquisition and took a one-time impairment charge of $319 million on the goodwill associated with the deal (see BioCentury, Nov. 13, 2006).

**Languishing stock**

OSI now gets the vast bulk of its revenue from Tarceva erlotinib, a small molecule inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase activity. It is approved for second-line treatment of advanced NSCLC and for first-line advanced pancreatic cancer.

But annual growth of OSI’s revenues from the drug have been decreasing — from 31% in 2007 to 25% in 2008 to 7% in 2009 — and an FDA panel voted 12-1 in December against adding an indication for first-line maintenance treatment for NSCLC (see “OSI Financials”).

Next in line is OSI-906, an insulin-like growth factor-1 (IGF-1) receptor inhibitor in Phase III testing to treat advanced adenocortical carcinoma and in Phase I/II to treat recurrent ovarian cancer in combination with paclitaxel. Both trials started last September.

Given the lack of drivers, OSI’s stock has spent the last four-plus years trading mostly in the $20-$40 range (see “OSI Chronicles,” A12).

Investors therefore were unhappy to learn last week that OSI’s board had turned down an offer from Astellas of $55-$57 in cash per share in February 2009.

Sven Borho of OrbiMed Advisors told BioCentury he was nonplussed with OSI’s decision not to take the money last year, given that the biotech’s shares have been

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**OSI financials**

Revenues related to OSI Pharmaceuticals Inc. (NASDAQ:OSIP). Tarceva revenue includes net revenue from its unconsolidated joint business related to OSI’s co-promotion and manufacturing agreement with Genentech Inc., Tarceva-related royalties and Tarceva-related milestones. (A) Net revenue from unconsolidated joint business plus Tarceva-related royalties. $M

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<th>Year</th>
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<th>Macugen rev</th>
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<td>$92 (A)</td>
<td>NA</td>
<td>$31 (U.S; 4Q)</td>
<td>NA</td>
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</tr>
</tbody>
</table>
It’s irritating that we didn’t know about the offer last year — $55 last year put in the general market would be about $75 now.”

Sven Borho, OrbiMed Advisors

Strategy, from previous page

flat while the market has rebounded.

Astellas’ initial offer was a 54-60% premium to OSI’s close of $35.60 on Jan. 30, 2009. On Feb. 26, 2010, the last trading day before Astellas announced it would begin a hostile offer at $52, the biotech’s stock price had risen only 4% to $37.02.

Over the same period, the S&P 500 was up 34%, the NYSE Arca Biotechnology index (BTK) was up 64% and the BioCentury 100 was up 22%.

“It’s irritating that we didn’t know about the offer last year. $55 last year put in the general market would be about $75 now,” Borho said. OrbiMed owns 1.7 million shares (3%) of OSI.

The March 1 announcement of the tender offer drove OSI’s shares up $19.23 (52%) to $56.25 on the day. OSI ended the week at $56.99.

“Nobody is tendering at $52,” Borho said. “If you’re considering that, then you might as well sell on the open market now that it’s over $56. Everyone understands that Astellas is committed to the deal, and this is an opening bid. If they bump it up, they will get shareholder support.”

Borho said OrbiMed values OSI at $60 per share, which includes revenues related to Tarceva, royalties from sales of dipeptidyl peptidase-4 (DPP-4) inhibitors to treat diabetes based on OSI’s patent estate, and OSI’s pipeline.

OSI’s FY09 revenues were $428.1 million, $358.7 million (84%) of which are related to Tarceva.

OSI and Roche’s Genentech Inc. unit co-market Tarceva in the U.S. and split net sales, while Roche markets it elsewhere in return for a 20% royalty.

It’s unclear how those sales will be split going forward. OSI and Genentech have an agreement under which the U.S. Tarceva sales force will be 50% OSI employees through 2010, so that agreement apparently will need to be renegotiated by year end.

Royalties on sales of DPP-4 inhibitors have ramped up, from $17 million in 2007 to $62 million in 2009. Five products incorporating DPP-4 inhibitors are on the market: Januvia sitagliptin and Janumet sitagliptin/metformin from Merck & Co. Inc.; Galvus vildagliptin and Eucrezas vildagliptin/metformin from Novartis AG; and Onglyza saxagliptin from Bristol-Myers Squibb.

Expanding Tarceva

Astellas’ offering price is 7.8 times the Street’s estimated 2010 revenues of $486 million for OSI. Whether that number turns out to be high or low depends in part on whether FDA ignores the December Oncologic Drugs Advisory Committee (ODAC) vote against first-line maintenance use of Tarceva in NSCLC.

The sNDA has an April 18 PDUFA date.

Although the drug met the Phase III SATURN trial’s co-primary endpoints of progression-free survival (PFS) vs. placebo in all patients and in a subgroup of patients determined to be EGFR mutation-positive, the panel said the one-month improvement in overall survival (OS) was not good enough to warrant approval (see BioCentury, Dec. 21, 2009).

OSI submitted additional data to FDA in January for the maintenance indication.

Although ODAC was not persuaded by the EGFR-mutation positive subgroup data, use in that subgroup still could result in an uptick in sales because the National Comprehensive Cancer Network (NCCN) updated its clinical practice guidelines in December to include Tarceva as a first-line treatment option for EGFR-mutation positive advanced or metastatic NSCLC patients.

Additionally, OSI and Roche’s Chugai Pharmaceutical Co. Ltd., subsidiary of Roche, are conducting a Phase II trial of Tarceva in Japan for first-line treatment of NSCLC patients with EGFR mutations. The company said about 30% of NSCLC patients of Asian origin have EGFR mutations compared with about 12% of Caucasian patients.

OSI is also running the Phase III RADIANT trial to study Tarceva as adjuvant treatment in early stage NSCLC patients who are EGFR-mutation positive. The company expects to complete enrolment of the 945-patient trial this half, but data won’t come out until 2013 or 2014.

OSI, Bayer AG and Onyx Pharmaceuticals Inc. are collaborating on a Phase III trial combining Tarceva and Nexavar sorafenib to treat advanced hepatocellular carcinoma (HCC). The trial is enrolling 700 patients. OSI would not disclose when it expects data.

Tarceva also is in two Phase III trials in Europe: an 830-patient ovarian cancer study which completed enrollment in 2008, with data expected in 2011; and a 640-patient study in combination with Avastin to treat colorectal cancer. OSI would not disclose when it expects data from the latter trial.

The biotech said there are more than 130 other investigator-sponsored trials of Tarceva ongoing in a variety of tumor types.

On OSI’s 2009 earnings call on Feb. 23, Goddard said the company’s NPV models suggest Tarceva will reach its peak value around the end of 2012 or 2013.

He added that if OSI is unable to grow the company’s overall NPV by moving beyond the “one drug company moniker” with acquisitions or new product approvals, then “we will change course towards monetizing the Tarceva asset as it approaches its peak value over the next several years.”

The biotech also has two cancer compounds in Phase I: OSI-027, an inhibitor of mammalian target of rapamycin (mTOR) kinase; and OSI-930, a dual receptor tyrosine kinase c-kit/VEGF receptor inhibitor. Because of the crowded VEGF receptor space, OSI is looking to partner out OSI-930, and granted exclusive Chinese rights to Simcere Pharmaceutical Group last October.

OSI also has three compounds in Phase I testing from its diabetes and obesity program: PSN602, a dual serotonin and norepinephrine reuptake inhibitor and 5-HT1A agonist; PSN821, a G protein-coupled receptor 119 (GPR119) agonist; and PSN010, a glucokinase activator (GKA).

Eli Lilly and Co. has an exclusive worldwide license to the GKA program, including PSN010, under a 2007 deal.

Astellas’ needs

When Astellas was formed in 2005 via the merger of Yamanouchi Pharmaceutical Co. Ltd. and Fujisawa Pharmaceutical Co. Ltd., subsidiary of Fujisawa, to incorporate DPP-4 inhibitors are on the market: Januvia, sold by Merck & Co.; Janumet, a sitagliptin and metformin combination; and Onglyza, a saxagliptin and metformin combination, sold by AstraZeneca.

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strategies, from previous page

tical Co. Ltd., the company said its strengths were in transplantation and urology.

In December 2006, the pharma decided to begin aggressively in-licensing and acquiring companies in order to expand into immunology and infectious disease, neurology, diabetes and metabolic diseases, and oncology.

The strategy has yet to bear fruit, as revenues were actually down in the company’s last fiscal year ended March 31, 2009. Net sales dropped by ¥6.9 billion, or 0.7%, to ¥965.7 billion ($9.9 billion) from the previous year. Astellas pinned most of the blame on foreign currency effect, but the company’s two leading products also lost sales due to generic competition.

Prograf tacrolimus and Harnal tamsulosin had combined sales of ¥317.6 billion, for 33% of Astellas’ FY09 sales.

Prograf, an immunosuppressant to suppress organ rejection in organ transplants, lost patent protection in the U.S. in April 2008 and in the EU in June 2009. Harnal, an adrenergic receptor alpha 1 (ADRA1) antagonist to treat benign prostatic hyperplasia (BPH), lost patent protection in the U.S. in October 2009, in the EU in 2006 and in Japan in 2005.

Boehringer Ingelheim GmbH and Astellas co-market tamsulosin as Flomax in the U.S.

Astellas’ third-best seller is Vesicare solifenacin succinate, a muscarinic receptor antagonist marketed to relieve symptoms associated with overactive bladder (OAB). Vesicare had ¥71.4 billion in sales for FY09, an increase of ¥11.3 billion (19%) from FY08.

GlaxoSmithKline plc and Astellas co-promote the drug in the U.S.

The pharma’s only cancer drug is Eligard leuprolide acetate to treat prostate cancer, which is marketed in the EU. Sales were €87 million ($115.5 million) for the year ended March 31, 2009. Astellas has EU rights to the atrigel drug delivery system to treat prostate cancer, which is marketed in the EU. Sales were down in the company’s last fiscal year ended March 31, 2009.

Astellas has €8.4 billion in sales from Prograf, its third-best seller.

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The Japanese company has one cancer compound in Phase III testing: MDV3100, a next generation androgen receptor antagonist for castration-resistant prostate cancer. Astellas received rights to the compound from Medivation Inc. last October. MDV3100 entered the Phase III AFFIRM trial last September.

Behind that are five oncology compounds in Phase II trials and four in Phase I.

In addition to providing a marketed cancer drug, the OSI acquisition would help Astellas’ U.S. footprint, which it needs to return to growth. The company’s $1.8 billion sales in 2009 came mostly from Japan (52.9%), followed by Europe (24.8%) and the U.S. (19.6%).

Borho noted it is difficult to grow sales in Japan because of the country’s universal pricing scheme, where the government cuts drug prices every two years.

“The best use of Japanese pharma’s money is not internal R&D or buying other companies at home in Japan, but going overseas. They will look at things that can get a lot of revenues with a small force, and cancer is a perfect way to enter the international market,” he said.

Astellas has already tried once to get into the U.S. market via a major acquisition, offering $1.1 billion in cash for CV Therapeutics Inc. in February 2009. The pharma dropped the bid the next month after Gilead offered $1.4 billion for the cardiovascular company.

Borho doesn’t think Roche will step in as OSI’s white knight. Because this is a strategic move for Astellas, he expects a larger premium than from a company like Roche, which he thinks would look at OSI from a purely financial standpoint.

But, Borho added: “You never know with Roche. If it makes sense for them financially then they might do it.”

COMPANIES AND INSTITUTIONS MENTIONED

Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan
Bayer AG (Xetra: BAY), Leverkusen, Germany
Boehringer Ingelheim GmbH, Ingelheim, Germany
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Chugai Pharmaceutical Co. Ltd. (Tokyo:4519), Tokyo, Japan
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.
Genentech Inc., South San Francisco, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
MediGene AG (Xetra:MDG), Martinsried, Germany
Medivation Inc. (NASDAQ:MDV), San Francisco, Calif.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Novartis AG (NYSE: NVS; SIX: NOVN), Basel, Switzerland
Onyx Pharmaceuticals Inc. (NASDAQ:ONXX), Emeryville, Calif.
OSI Pharmaceuticals Inc. (NASDAQ:OSIP), Melville, N.Y.
Roche (SIX: ROG; OTCQX: RHHBY), Basel, Switzerland
Sincere Pharmaceutical Group (NYSE:SCR), Nanjing, China

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Garnet Bio B8

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**OSI chronicles**

- **A. 2/25/00** — Raises $56.5M in a PIPE
- **B. 6/19/00** — Gets full rights to Tarceva from Pfizer Inc. (NYSE:PFE), which enabled the pharma to satisfy FTC requirements for its merger with Warner-Lambert Co. The compound was identified under a 1986 cancer collaboration between OSI and Pfizer.
- **C. 11/1/00** — Raises $430.7M in a follow-on
- **D. 1/8/01** — Licenses Tarceva to Genentech Inc. and Roche (SIX:ROG; OTCQX:RHHBY)
- **E. 11/26/01** — Says it will acquire oncology assets, including three compounds and a Boulder, Colo., facility, from Gilead Sciences Inc. (NASDAQ:GILD) for up to $200M. The most advanced oncology candidate, NX211 (OSI-211) liposomal lurtotecan, was in Phase II testing to treat solid tumors at the time of the deal. The company stopped development of NX211 in 2004.
- **F. 1/29/02** — Raises $200M in a convertible notes offering
- **G. 10/24/02** — Says it will cut headcount to about 450 from 490 and would look to divest certain non-oncology research assets by establishing an externally funded entity focused on metabolic diseases
- **H. 2/10/03** — Says it will acquire cancer company Cell Pathways for about $2M in stock. OSI gains NSCLC compound Aptsyn exisulind.
- **I. 3/12/03** — Says it will pay $55M in initial fees plus maintenance fees for U.S. marketing rights to Novantrone mitoxantrone from Serono S.A., now part of Merck KGaA (Xetra:MRK). Novantrone is approved to treat acute non-lymphocytic leukemia (ANLL), pain associated with advanced hormone-refractory prostate cancer, and certain advanced forms of multiple sclerosis.
- **J. 9/3/03** — Raises $135M in a convertible debt offering
- **K. 10/1/03** — Tarceva plus chemotherapy misses the primary endpoint as first-line therapy in two Phase III studies (TRIBUTE and TALENT) in metastatic non-small cell lung cancer (NSCLC)
- **L. 4/26/04** — Tarceva meets the primary endpoint in a Phase III study in recurrent NSCLC
- **M. 6/11/04** — Aptsyn exisulind misses the primary endpoint in a Phase III trial in NSCLC
- **N. 11/10/04** — Raises $387M in a follow-on
- **O. 11/18/04** — FDA approves Tarceva to treat locally advanced or metastatic NSCLC in patients who have failed chemotherapy
- **P. 8/22/05** — Shares drop 22% to $31.82 after the company says it will buy Eyetech for $935M, including $701M in cash and $234M in stock. OSI gains Macugen pegaptanib for AMD.
- **Q. 9/21/05** — EU approves Tarceva to treat locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen
- **R. 11/2/05** — FDA approves Tarceva to treat advanced or metastatic pancreatic cancer in chemotherapy-naive patients
- **S. 12/16/05** — Raises $100M in a convertible notes offering
- **T. 11/6/06** — Says it will exit the eye disease business and will out-license, partner or sell Macugen pegaptanib
- **U. 1/29/07** — Europe approves Tarceva to treat metastatic pancreatic cancer in combination with gemcitabine
- **V. 11/14/07** — Tarceva plus Avastin bevacizumab and gemcitabine misses the primary endpoint in the Phase III AVITA trial to treat metastatic pancreatic cancer
- **W. 1/4/08** — Raises $175M in a convertible notes offering
- **X. 10/6/08** — Tarceva plus Avastin misses the primary endpoint in the Phase III BeTa Lung trial to treat metastatic NSCLC
- **Y. 12/16/09** — FDA panel votes 12-1 against recommending approval of an sNDA for Tarceva for first-line maintenance treatment of advanced or metastatic NSCLC
- **Z. 3/1/10** — Astellas announces an unsolicited tender offer to acquire OSI for $52 per share, or about $3.5B
Emerging Company Profile

Virdante: Superpowering sialylation

By Michael Flanagan
Senior Writer

Intravenous immune globulin products provide symptomatic relief for autoimmune and inflammatory conditions when given at high doses. Virdante Pharmaceuticals Inc. is developing an IVIG product that is 10 times more potent in preclinical models, which could provide advantages in dosing, cost of goods and tolerability.

Virdante was founded by Jeffrey Ravetch, an immunology professor at Rockefeller University, based on 10 years of research designed to better understand and ultimately improve upon IVIG, a plasma-derived product containing pooled IgG antibodies.

According to CEO John Ripple, Ravetch became interested in IVIG because of its paradoxical mechanism. When given at low doses, the drug produces pro-inflammatory effects in patients with immune deficiencies, but high doses have anti-inflammatory properties and provide symptomatic relief for patients with autoimmune or inflammatory conditions.

According to Ripple, the majority of IVIG use is for autoimmune and inflammatory conditions such as chronic inflammatory demyelinating polyneuropathy (CIDP) and immune thrombocytopenic purpura (ITP). The IVIG market surpassed $4 billion in sales during 2008 and has been growing in the high single digits annually, he noted.

"Ravetch hypothesized that IVIG has both pro- and anti-inflammatory properties because it is a polyclonal mixture of antibodies, so while the vast majority of the IgG antibodies are pro-inflammatory, there must be a certain subpopulation with anti-inflammatory properties," said Ripple.

In 2006, the Rockefeller team published a study in Science describing the discovery of a small population of IgG antibodies with a sialic acid on the terminal end of the Fc-linked glycans that have anti-inflammatory properties. The group also reported that IgG antibodies lacking sialic acid generated pro-inflammatory effects and, critically, that these effects could be switched to anti-inflammatory simply by sialylating (adding a sialic acid to) their Fc portion.

Virdante was founded in 2007 and has exclusive rights to the Sialic Switch technology, which Ripple said uses a simple and scalable enzymatic glycosylation process to sialylate the Fc-linked glycans that are lacking sialic acid.

"The technology essentially acts as a secondary manufacturing process in which we can take the heterogeneous IVIG product, apply a straightforward biochemical process using an enzyme and sugar nucleotide, and end up with the homogeneous drug product with much better anti-inflammatory potency," he said.

Using Sialic Switch, Virdante has developed a sialylated version of IVIG (sIVIG) with improved potency. "We have demonstrated in preclinical models that a tenfold lower dose of sIVIG provides benefits comparable with marketed IVIG," said Ripple. This could provide advantages in terms of patient convenience and compliance, cost of goods (COGS) and tolerability.

Patients with autoimmune or inflammatory conditions are given 2 g/kg of existing IVIG products, "meaning that a 100-kg patient needs to take a 200 g dose on a periodic basis, typically every month, with each dose having to be given intravenously for up to five days," he noted.

Ripple said it is too early to estimate what sort of savings the sIVIG product could provide in terms of lower COGS. "When we look for a commercial partner prior to conducting the registration studies, one thing we will be able to offer is strategic flexibility. Because of the more anti-inflammatory effects, our partner could take either a premium pricing or a penetration pricing approach," he said.

Ripple added: "Adverse events associated with IVIG, though rare, are often due to the volume of drug that must be infused or the load of protein that is being delivered, which we would be able to decrease tenfold with sIVIG."

The labels for marketed IVIG products contain warnings about risk of renal failure, hyperproteinemia and thrombotic events.

Ripple declined to provide a timeline for moving the sIVIG program into the clinic, though he noted that a $47.8 million series A round that closed in October should be sufficient to see Virdante through to proof-of-concept (POC) data in humans.

Ripple also hopes to use the Sialic Switch technology to develop a sialylated version of a recombinant Fc fragment (rFc). "Rather than using the entire IgG antibody from IVIG, we would take just the Fc fragment and produce it recombinantly, so it would be much smaller and produce more potent anti-inflammatory effects on a per-mass basis," he said.

Ripple also believes the technology has the potential to enhance the anti-inflammatory properties of marketed antibody products, such as one of the anti-TNF mAbs, "which only work well in a third of patients, while in the remainder they have little or no effect."

Companies or Institutions Mentioned

Rockefeller University, New York, N.Y.
Hope trumps doubts on belatacept

By Erin McCallister
Senior Writer

The need for an alternative to calcineurin inhibitors was enough to sway an FDA panel that belatacept from Bristol-Myers Squibb Co. deserves to be approved to prevent organ rejection in renal transplant patients, despite concerns about the compound’s efficacy and safety.

Last week, FDA’s Cardiovascular and Renal Drugs Advisory Committee voted 13-5 that belatacept had a positive benefit-risk profile for the prevention of organ rejection in renal transplant recipients.

Panel members did have concerns about FDA’s reanalysis of data from the Phase III trials, which showed belatacept was numerically worse than cyclosporine in preventing acute rejections. However, because belatacept fell within the 20% noninferiority margin established by the agency, they agreed it demonstrated efficacy.

The committee also was concerned about the rates of post-transplant lymphoproliferative disorder (PTLD) and progressive multifocal leukoencephalopathy (PML) in the belatacept arms of Phase II and Phase III trials.

On the other hand, the panel was impressed with belatacept’s improvement of glomerular filtration rate (GFR) compared to cyclosporine — an endpoint FDA agreed to in an SPA but then reneged after the trial was underway.

Given the tradeoffs, the panel endorsed belatacept for use in a restricted population, and only if a strict patient registry was put in place to monitor the rates of PTLD and PML.

Benefits vs. tox

About 17,000 kidney transplants are performed in the U.S. each year. To prevent graft loss, patients must take a series of immunosuppressants.

The standard of care for prevention of rejection is a calcineurin inhibitor (CNI), such as cyclosporine, in combination with an IL-2 receptor antagonist, CellCept mycophenolate mofetil from Roche and corticosteroids.

CNIs are not approved to preserve a functioning allograft.

BMS is seeking approval of belatacept for prevention of graft rejection and preservation of a functioning allograft as an alternative to CNIs.

Since CNIs were first introduced more than 20 years ago, short-term outcomes for transplant patients have improved. Immunosuppressive regimens that include CNIs have one-year graft survival rates of 90% for deceased donor grafts and 95% for recipients of living donor grafts, with acute rejection rates of 10-20% during the first year of transplant.

Acute rejection generally occurs within the first three months after transplant but rarely results in the loss of the graft. It generally manifests in symptoms including an unexplained rise in serum creatinine >25% from baseline, unexplained decrease in urine output, fever and graft tenderness, and serum creatinine that remains elevated within 14 days of transplant.

Due to toxic side effects of CNIs, however, long-term outcomes are not as good. CNIs are associated with renal, cardiovascular and metabolic toxicities, which can cause renal impairment, hypertension, hypercholesterolemia and diabetes.

According to BMS, CNIs have 5- and 10-year rates of patient survival with a functioning graft of 68% and 39% for recipients of deceased donor transplants and 80% and 57% for recipients of living donor transplants. The main driver of these figures is death, commonly due to CV disease, and renal dysfunction due to chronic allograft nephropathy.

These toxicities are attributed to calcineurin’s ubiquitous distribution in many cellular pathways.

The goal of the belatacept program was thus to achieve the short-term benefits of CNIs with fewer of the off-target CV, renal and metabolic effects that lead to long-term graft loss and mortality.

Belatacept is a recombinant soluble fusion protein consisting of an extracellular domain of human CTLA-4 and an Fc domain of human IgG. The CTLA-4 portion competes with CD28 for binding to CD80/86 (B7-1/B7-2) on antigen presenting cells, thus disrupting costimulatory signaling that would result in the activation of T cells against the graft.

Per protocol

BMS’s submission was based on results from two three-year Phase III trials comparing belatacept vs. cyclosporine: Study IM103008 and Study IM103027. Both studies assessed two dosing regimens: more intensive (MI) and less intensive (LI) (see “Belatacept Trial Designs,” A15).

Study ‘008 had two primary endpoints: noninferiority to cyclosporine on the composite of patient and graft survival, and superiority to cyclosporine on renal impairment measured by GFR.

According to BMS’s briefing documents, the company selected GFR because it believed an improvement would translate into long-term preservation of graft survival. Several studies in the literature have shown that renal function is the strongest determinant of long-term graft survival, CV events and transplant recipient mortality.

The ‘008 trial used the same two primary endpoints as Study ‘027, plus a third primary endpoint of noninferiority to cyclosporine for incidence of acute rejection, which was a secondary endpoint in the ‘027 trial.

All patients in the trials were biopsied. But BMS’s analysis of acute rejection included only patients who both showed clinical symptoms and had a positive biopsy.

BMS received an SPA from FDA in 2005 for Study ‘008, indicating that cyclosporine was the appropriate comparator and that the endpoints were appropriate.

The company set a 10% noninferiority margin for the patient
and graft survival endpoint based on consultation with FDA. Similarly, the company selected a noninferiority margin of 20% for the acute rejection endpoint.

In both studies, belatacept was noninferior to cyclosporine on patient and graft survival.

Belatacept was statistically superior to cyclosporine on the difference in patients meeting the renal endpoint of GFR in Study ‘008. In Study ‘027, both regimens of belatacept were numerically superior to cyclosporine on this endpoint, but only the MI regimen was statistically superior.

On the final primary endpoint of acute rejection in the ‘008 trial, cyclosporine had numerically better rates, but both doses of belatacept fell within the 20% noninferiority margin.

Belatacept also demonstrated improvements over cyclosporine on metabolic and cardiovascular endpoints, including blood pressure, triglycerides, and the incidence of new onset diabetes (see “Hope for Survival,” A16).

BMS is seeking approval for belatacept as dosed under the LI regimen, based on its safety profile.

The primary debate

While FDA agreed to the composite endpoints of graft loss or death and GFR for Study ‘008 as part of the SPA in 2005, the agency had changed its mind by the time it reviewed the NDA (see “Parting Ways on Efficacy,” A17).

According to FDA’s briefing documents, acute rejection is the best endpoint to assess short-term benefits because CNIs and other immunosuppressants have improved patient and graft survival in the first year.

The agency also decided it was not comfortable with GFR as a surrogate endpoint for renal impairment in a trial with cyclosporine as the comparator. Cyclosporine causes vasoconstriction of the afferent renal artery, which causes an immediate decrease in GFR. The agency thus felt the hemodynamic effects of cyclosporine confounded the GFR results.

Even though some patients in the belatacept arm achieved an increase in GFR, the agency concluded there was not enough information to attribute an increase in or maintenance of GFR to belatacept. According to the agency, a study of cyclosporine plus belatacept vs. cyclosporine alone would be needed to substantiate that outcome.

FDA did acknowledge the importance of GFR in maintaining renal function and considered the GFR data as part of its safety analysis.

Based on its issues with the composite endpoints in BMS’s trials, the agency decided to reanalyze the data with biopsy-proven acute rejection (BPAR), graft loss and death as the composite primary endpoint. In its briefing documents, the agency noted that this composite endpoint was used in previous approvals of drugs for the same indication.

FDA’s analysis of BPAR included all patients with positive biopsy, whether they had clinical symptoms or not. As a result, the agency’s analysis of acute rejection included more patients than did the BMS assessment.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Patients</th>
<th>Primary endpoints</th>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM103027</td>
<td>Recipients of kidneys from deceased donors considered high risk, including organs from donors older than 60 or from donors who had died of cardiac causes, and/or organs that were transplanted 24 hours or more after they were procured</td>
<td>543</td>
<td>NI on the composite of patient and graft survival at 12 months; superiority on renal impairment defined as GFR &lt;60 mL/min/1.73m² at month 12 or a decrease in measured GFR ≥ 10 mL/min/1.73m² from month 3 to month 12</td>
<td>NI on incidence of acute rejection at 12 months determined by clinical symptoms and positive biopsy</td>
</tr>
<tr>
<td>IM103008</td>
<td>Recipients of kidneys from living donors and kidneys from deceased donors not considered high risk</td>
<td>666</td>
<td>Above, plus NI on incidence of acute rejection determined by clinical symptoms and positive biopsy</td>
<td>Measured GFR; biopsy-proven chronic allograft nephropathy; systolic and diastolic blood pressure; non-HDL cholesterol, LDL cholesterol and triglycerides; new onset diabetes</td>
</tr>
</tbody>
</table>

Bristol-Myers Squibb Co. (NYSE:BMY) based its BLA for belatacept on results from two three-year Phase III trials designed to show the fusion protein was noninferior to cyclosporine on the short-term measures of 12-month patient and graft survival, and superior to cyclosporine on glomerular filtration rate (GFR), a measure of renal impairment believed to be correlated with long-term graft survival. Both studies assessed more intensive (MI) and less intensive (LI) dosing regimens. The MI regimen consisted of 10 mg/kg on the day of transplant, day 5, day 14 and every 14 days out to day 84, then every 4 weeks through six months. At month 7, patients were put on a maintenance dose of 5 mg/kg every four weeks. The LI regimen consisted of 10 mg/kg on the day of transplant, day 5, day 14, day 28, month 2 and month 3. After month 3, patients were put on the same maintenance schedule as the MI regimen.

Cyclosporine was dosed twice daily to achieve trough concentrations of 150-300 ng/ml during the first month after transplant, and 100-250 ng/ml thereafter. Patients in all treatment arms also received an IL-2 receptor antagonist at induction and CellCept mycophenolate mofetil plus corticosteroids during maintenance. CellCept is marketed by Roche (SIX:ROG; OTCQX:RHHBY). Despite an SPA covering Study ‘008, BMS and FDA wound up disagreeing on the appropriate endpoints for the trials.
By FDA's analysis, belatacept LI met the 20% noninferiority margin for BPAR, but cyclosporine was numerically superior.

Hope and noninferiority

Most panel members agreed that belatacept was noninferior, even if it did not perform better than cyclosporine when it came to BPAR, graft loss and death. But some statisticians on the panel even if it did not perform better than cyclosporine when it came to BPAR, graft loss and death. But some statisticians on the panel argued the agency had set the bar too low.

"It bothers me that FDA is most comfortable with the 20% noninferiority margin," said Michael Proschan, a temporary member and a statistician in the biostatistics research branch at NIH’s National Institute of Allergy and Infectious Diseases (NIAID). He voted against approval.

Sanjay Kaul, director of the cardiovascular disease fellowship training program at Cedars-Sinai Heart Institute and a permanent voting member, said the margin was too wide because it translated into an upper limit of 2 on the hazard ratio for BPAR, translating into the possibility of a 100% greater likelihood of BPAR, graft loss or death with belatacept vs. cyclosporine.

"Is 100% worsening acceptable? I have yet to hear a compelling argument of why we should accept that," Kaul said. He also voted against approval.

While the panel was disappointed with belatacept’s performance on the acute rejection endpoint, members were intrigued by its potential to improve GFR.

“What we’re faced with here is hope that this will provide long-term graft survival,” said Richard Mann, a temporary voting member and an associate professor of medicine in the department of nephrology at the Robert Wood Johnson Medical School. “Would I accept higher [acute] rejection from an agent that will give longer term survival? Absolutely.”

Mann also differed with the agency’s interpretation of the GFR dynamics. While the agency is correct that cyclosporine causes arterial constriction and therefore an immediate reduction in GFR, he pointed out the CNI can lead to kidney damage in the long term.

“Over time, you will see damage to the organ. While the hemodynamic effect will disappear if you take them off of a calcineurin inhibitor, it doesn’t mean that there isn’t intrinsic damage.”

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Hope for survival

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Study '008</th>
<th>Study '027</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-value</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Improvement in mean GFR at month 12 vs. cyclosporine</td>
<td>14.6 units</td>
<td>13 units</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rate of GFR decline from month 3 to month 24 (mL/min/1.73m²/yr) (A)</td>
<td>+0.96</td>
<td>+1.19</td>
</tr>
</tbody>
</table>

Secondary metabolic/cardiovascular endpoints

<table>
<thead>
<tr>
<th></th>
<th>Study '008</th>
<th>Study '027</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure - mean at month 12</td>
<td>132.7</td>
<td>140.9</td>
</tr>
<tr>
<td>Diastolic blood pressure - mean at month 12</td>
<td>79.3</td>
<td>78.3</td>
</tr>
<tr>
<td>Non-HDL cholesterol - mean at month 12</td>
<td>131.7</td>
<td>134.4</td>
</tr>
<tr>
<td>LDL cholesterol - mean at month 12</td>
<td>100.8</td>
<td>102.5</td>
</tr>
<tr>
<td>Triglycerides - mean at month 12</td>
<td>155</td>
<td>152.9</td>
</tr>
<tr>
<td>New onset diabetes after transplant at month 12 v. no diabetes at transplant</td>
<td>11/156 (7.1%)</td>
<td>11/118 (9.3%)</td>
</tr>
</tbody>
</table>
damage,” he said.

Mann and other transplant physicians on the panel also endorsed belatacept because it provided an alternative to CNIs.

“All I see is that this tool gives transplanting physicians flexibility in managing difficult patients who cannot take calcineurin inhibitors,” said Douglas Hale, a temporary voting member and an associate professor of surgery at Vanderbilt University Medical Center.

Hale told BioCentury that hemolytic uremic syndrome and thrombotic microangiopathy are serious complications associated with CNIs, with an incidence of 1-5%, and that there are no alternatives that avoid these complications.

He added there also is a small number of patients who cannot tolerate the side effects of CNIs, including hyperkalemia, tremor, headache, gingival hyperplasia and hirsutism.

Other panel members were swayed by the metabolic and cardiovascular benefits of belatacept.

“To me, efficacy benefits also include changes in GFR and the potential benefits that might provide, plus a reduced prevalence of diabetes,” Juergen Venitz said. Venitz is an associate professor in the department of pharmaceutics at the Medical College of Virginia.

Allan Sampson, professor of statistics at the University of Pittsburgh, agreed: “If you overlay cardiovascular, lipid and diabetes impacts, it looks positive to me.”

Venitz and Sampson are temporary voting members.

Five of the six transplant and/or nephrology experts on the panel voted in favor of belatacept.

### Safety first

While the panel supported approval, it recommended a patient registry to monitor for cases of PTLD and PML, which occurred at a higher rate in the belatacept arms of Phase II and Phase III trials.

PTLD is a complication of solid organ and allogeneic bone marrow transplant. It is a group of B cell lymphomas that occur in immunosuppressed patients and tends to occur following infection with Epstein-Barr virus (EBV).

PTLD in the belatacept arms predominately had CNS involvement.

The highest occurrence of PTLD was in the MI regimen, which had 8 cases across the trials, 6 of which occurred in patients who were serologically negative for EBV or whose EBV status was unknown. The belatacept LI arm had 6 cases of PTLD, including 2 in EBV-negative patients.

There were 2 cases of PTLD in the cyclosporine arm. One was EBV-negative, and the other’s EBV status was unknown.

BMS and FDA hypothesized that one reason for the increased rate of PTLD in the belatacept arms was the use of lymphocyte-

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### Parting ways on efficacy

Bristol-Myers Squibb Co. (NYSE:BMY) and FDA took different approaches to analyzing the Phase III trials of belatacept, despite an SPA covering Study ’08. Members of the Cardiovascular and Renal Drugs Advisory Committee found merits in both approaches, and voted 13-5 in favor of approving the compound to prevent organ rejection in kidney transplant, but only for a restricted population, and only if a strict registry is created to monitor for safety problems. BMS analyzed two primary endpoints in Study ’027 and three in Study ’008. In both trials, both the more intensive (MI) and less intensive (LI) dosing regimens of belatacept met the primary endpoint of noninferiority to cyclosporine on the composite of patient and graft survival. MI and LI belatacept were statistically superior to cyclosporine on the primary endpoint measuring renal impairment in Study ’008. In Study ’027, both regimens of belatacept were numerically superior to cyclosporine on renal impairment, but only the MI regimen was statistically superior.

On the final primary endpoint of acute rejection in Study ’008, both MI and LI belatacept fell within the 20% noninferiority margin, but cyclosporine had fewer cases of acute rejection than either regimen of belatacept. According to BMS’s briefing documents, of the patients in the belatacept arms who experienced acute rejection in the two Phase III trials, 8 resulted in graft loss vs. 5 for cyclosporine, and 4 resulted in death vs. 2 for cyclosporine. FDA asked the panel to vote on the efficacy of belatacept based on a composite endpoint the agency calculated after the trials were complete: biopsy-proven acute rejection (BPAR), graft loss and death. While belatacept was numerically worse than cyclosporine on this endpoint, it still met the 20% noninferiority margin set by the agency. FDA considered the renal impairment data as part of its safety review. **Source: FDA briefing documents**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Study ’008</th>
<th>Study ’027</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient and graft survival at 12 mos</td>
<td>95.0% [1.8 -3.6, 7.2]</td>
<td>96.5% [3.3 - 1.8, 8.4]</td>
</tr>
<tr>
<td>Difference from cyclosporine [97.3% CI]</td>
<td>57.1% &lt;0.0001</td>
<td>56.6% &lt;0.0001</td>
</tr>
<tr>
<td>Patients with renal impairment</td>
<td>22.4% [7.4, 23.0]</td>
<td>17.3% [10.1, 2.9, 17.3]</td>
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<tr>
<td>Difference from cyclosporine [97.3% CI]</td>
<td>15.2 [10.7, 19.8]</td>
<td>5.5 [2.7, 13.7]</td>
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ANALYSIS

COVER STORY
A new spin on protegrin
University of Zurich and Polyphor researchers have developed protein epitope mimetics of the peptide protegrin I that specifically target Pseudomonas aeruginosa via a previously unknown mechanism of action. The biotech expects its lead mimetic to enter Phase I testing this year.

TARGETS & MECHANISMS
Casting a lure for EGFR ligands
U.S. researchers have identified an EGFR-mimicking peptide that blocks tumor growth by luring ligands away from the receptor, thus preventing its activation. The decoy could have advantages over marketed EGFR inhibitors, although its pharmacokinetic and toxicity profiles will have to be worked out first.

Interfering with integrins in atherosclerosis
University of North Carolina researchers have shown that a mAb targeting integrin αvβ3 blocks progression of diabetes-associated atherosclerosis in pigs. Vascular Pharmaceuticals is developing a humanized version of the antibody with support from Johnson & Johnson.

TOOLS
The leading edge on tumors
UCSD researchers have developed a method for visualizing tumor margins in vivo that could help improve tumor resection surgery and postoperative assessment. To commercialize the technology, the researchers have founded Avelas Biosciences, which is now gearing up for Phase I studies.

THE DISTILLERY
This week in therapeutics
Reducing reperfusion injury with meclizine; treating nerve damage with cyclosporin A; using IL-17A inhibitors to treat idiopathic pulmonary fibrosis; preventing hepatic GvHD with GAS6 inhibitors; and more...

This week in techniques
A cynomolgus macaque model of Chikungunya disease; multilayered capsules for in vivo bone formation; tumor-targeted imaging agents for cancer surgery; and more...

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Regulation, from previous page
depleting agents to treat acute rejection reactions. However, the agency cautioned that the overall contribution of these treatments to the development of PTLD is unknown.

There also was one case of PML reported in the belatacept MI arm of Study ‘008. There were no cases of PML reported for the LI regimen or cyclosporine. The incidence of PML in the general kidney transplant population is about 14 cases per 100,000 patient-years.

There also was one case of PML reported in the Phase II program for belatacept in liver transplant.

To mitigate the likelihood of increased cases of PTLD, BMS proposed belatacept be administered only to EBV-positive patients. The company provided a draft REMS that included a communication plan, a medication guide and postmarketing studies to characterize the incidence of PTLD in the transplant population.

The panel recommended that BMS also be required to include a strict patient registry to limit access to belatacept.

Elaine Morrato, assistant professor in the department of pediatrics at the University of Colorado, argued that a registry should not only track who receives the drug, but also ensure it is being used properly.

“I see a registry as being very important. We also need to understand how the drug is being institutionalized and whether or not the serotyping is being done uniformly across centers,” said Morrato, who is a temporary voting member.

For Hale, the increased incidence of PTLD was a fact of life in working with immunosuppressants.

“Every time we give a patient [immunosuppressants] that deplete their immune system, we are engaging in a form of therapy that increases the odds of PTLD,” he said. “Following these patients closely and restricting access to EBV-positive patients and using the FDA’s safety authority to track these patients is sufficient to assure that something really bad doesn’t happen.”

The panel supported approval of the LI regimen of belatacept for EBV-positive patients.

Neither BMS nor FDA would comment on why the preservation indication was not considered for a vote.

Belatacept has a May 1 PDUFA date.

COMPANIES AND INSTITUTIONS MENTIONED
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Cedars-Sinai Heart Institute, Los Angeles, Calif.
Medical College of Virginia, Richmond, Va.
National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, Md.
Robert Wood Johnson Medical School, New Brunswick, N.J.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
University of Colorado, Denver, Colo.
University of Pittsburgh, Pittsburgh, Pa.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.
Vanderbilt University Medical Center, Nashville, Tenn.
Archimedes looks to America

By Mike Ward
& Stacy Lawrence
Senior Writers

Novo Growth Equity, which was created last year, has made its first investment by putting £40 million into a £65 million ($98.4 million) round by Archimedes Pharma Ltd., on the condition that the specialty pharma play build a U.S. presence.

"Archimedes fits into our strategy of investing in companies that have late-stage de-risked assets. We asked whether the world needed another fentanyl product and we concluded that Archimedes’ product is differentiated enough," Novo’s Ulrik Spork told Ebb & Flow.

PecFent fentanyl nasal spray, which uses the company’s PecSys nasal drug delivery system, is under review in the U.S. and EU to treat breakthrough cancer pain. "With Growth Equity we are looking for up to a 3X return, while with our venture activities we are seeking up to 5X. We look to get at least a 15% holding, which will secure a board seat, but no more than 49%. This investment is within that range," Spork said.

Warburg Pincus, which had been the specialty pharma’s sole backer, provided the balance of the financing. To date, Archimedes has secured £133 million in funds.

Novo agreed to participate in the financing after it persuaded Warburg Pincus and Archimedes to modify their company building strategy to include establishing a U.S. commercial presence. "The original business plan called for Archimedes to find a single partner for the U.S. market. Our view is that the company can do this for itself," said Spork.

"This round is very much about maximizing the potential of the asset rather than out-licensing for the U.S. market, where we would have got less good economics and lost control."

Simon Turton, Warburg Pincus

Anthera acquiesces

Anthera Pharmaceuticals Inc. (NASDAQ:ANTH) eked out an IPO last Monday, raising $42 million through the sale of 6 million shares at $7. The price values the company at $151.1 million.

The prior week, the pulmonary and inflammation company lowered the price from $13-$15 to $8-$9 and then again to $7.

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while increasing the number of shares to 6 million from 4.6 million. At the $14 mid-point of the original range and 4.6 million shares, the company would have raised $64.5 million and been valued at $242.2 million.

Underwriters were Deutsche Bank; Piper Jaffray; Cowen; and Merriman Curhan Ford.

The company plans to begin Phase III testing of varespladib methyl (A-002) to treat acute coronary syndrome following the completion of the IPO. It has rights outside of Japan to the secretory phospholipase A2 (PLA2) inhibitor from Eli Lilly and Co. (NYSE:LLY) and Shionogi & Co. Ltd. (Tokyo:4507; Osaka:4507).

Anthera was up $0.01 to $7 in its first day of trading. On the week, the shares remained unchanged at $7.

Royalty engine

NPS Pharmaceuticals Inc. (NASDAQ:NPSP) last week sold off royalties for Regpara cinacalcet in Japan and other Asian countries to DRI Capital for $38.4 million to help finance two ongoing Phase III trials.

NPS earns Regpara royalties from partner Kyowa (Tokyo:4151), which markets the second-generation calcimimetic in Japan to treat secondary hyperparathyroidism during maintenance dialysis.

In the first three quarters of 2009, NPS received $2.6 million in royalties from Kyowa, which started marketing Regpara in 2H08.

NPS expects to report it had $70-$75 million in cash at Dec. 31 when it announces its 4Q results on March 11. It guided to a cash burn of $43-$50 million for 2009, but President and CEO Francois Nader told Ebb & Flow he expects the burn to increase this year due to the Phase III trials.

The company plans to complete Phase III enrollment for Gattex teduglutide (ALX-0600) to treat short bowel syndrome (SBS) by the end of this quarter and for NPSP558 (PTH 1-84) to treat hypoparathyroidism by mid-2010.

Top line Phase III data for Gattex are expected by year end or early 2011. Data for NPSP558 should be available by the end of 1Q11. If the data are positive, filings would follow in mid- and early 2011. Data for NPSP558 should be available by the end of 1Q11. If the data are positive, filings would follow in mid- and early 2011.

The company has rights outside North America to Gattex to treat gastrointestinal disorders, while NPSP558 remains unpartnered. Nycoderm and NPS are splitting Gattex development costs 50/50. Nycoderm already markets NPS’s NPSP558 as Preotact recombinant human parathyroid hormone (PTH) in Europe for postmenopausal osteoporosis.

Royalties return

This is NPS’s third royalty deal. It sold the Preotact royalties from Nycoderm to DRI (then Drug Royalty Corp.) for $50 million in 2007. It also has two non-recourse debt notes from an undisclosed investor. The notes are secured by royalty revenue NPS receives for Sensipar (Mimpara-EU) cinacalcet from Amgen Inc. (NASDAQ:AMGN).

In the first nine months of 2009, NPS received $7 million in Preotact royalties and $47.5 million in Sensipar royalties. At Sept. 30, $253.7 million in principal was outstanding on the two debt notes.

All three royalty deals have a ceiling above which royalties return to NPS, according to Nader. For the two DRI deals it is 2.5X the initial investment, and for the debt it is upon full repayment of principal.

Nader said it’s possible that Preotact and Regpara royalties would revert to NPS, but probably after 2015. Patents for the products expire in 2017 and 2020, respectively.

Nader does anticipate the return of the Sensipar royalties to NPS in early 2013, once the loans are fully repaid. He added the product should have patent protection through 2017.

On the week, NPS rose $0.65 (19%) to $3.99.

Many happy returns

Encore Ventures, a division of the European venture capital firm DFJ Esprit, has achieved an early return on its investment in the former 3i plc European venture portfolio through the $330 million sale of medical device company ApaTech plc to Baxter International Inc. (NYSE:BAX).

The Baxter deal put Encore in line to get more than three-quarters of the £130 million it paid for 29 companies that belonged to 3i last October. Encore owns 45% of ApaTech and thus could receive up to £100 million ($148 million). The deal involves a $240 million upfront cash payment from Baxter, with an earn-out of $90 million.

Another big winner is U.K. early stage investor MTI Partners. MTI had already gotten back its original £4.5 million investment in ApaTech’s 2004 series B round when it sold some of its stake in the next round in 2008, a $45 million financing that the company called a development capital round. Last week’s transaction gives MTI another $26.4 million.

HealthCor Partners, the U.S. VC that participated in the 2008 round, will be in line for a $59 million payday, while London’s Queen Mary College will receive up to $33 million. ApaTech’s founders, management and directors will get a further $63 million.

LP tracks

Janine Guillot joined the California Public Employees’ Retirement System (CalPERS) as chief operating investment officer. She will report to CIO Joseph Dear and be responsible for the alternative investment (AIM), real estate and public market portfolios. She was managing director and COO for the global fixed income business at Barclays Global Investors, which was acquired by BlackRock in December 2009.

Analyst tracks

Mark Schoenebaum is joining International Strategy & Investment (IIS) as head of healthcare research covering biotech, pharma and specialty pharma. He is leaving Deutsche Bank, where he was a managing director and head of biotechnology equity research.

Biren Amin joined WJB Capital as healthcare sector strategist. He was a biotech analyst with FTN Equity Capital Markets, which shuttered its equity research business last month.

PE tracks

Charles Stiefel joined private equity firm RoundTable.
Healthcare Partners as a senior advisor. He was chairman and CEO of dermatology company Stiefel Laboratories Inc., which was acquired last year for $2.9 billion in cash and $300 million in milestones by GlaxoSmithKline plc (LSE:GSK; NYSE:GSK).

Regulatory milestones

Adventrx Pharmaceuticals Inc. (NYSE-A:ANX) fell $0.09 (30%) to $0.20 on Monday after FDA refused to file an NDA for ANX-530 to treat non-small cell lung cancer (NSCLC) because of a problem with CMC data from the intended commercial manufacturing site. The stock was off $0.07 (24%) to $0.22 for the week.

Amgen Inc. (NASDAQ:AMGN) gained $0.63 to $57.24 last week after the U.K.’s NICE issued a preliminary appraisal for five drugs to treat rheumatoid arthritis after failure on a TNF inhibitor. NICE reiterated recommendations in favor of MabThera rituximab, a mAb against CD20 from Roche (SIX:ROG; OTCQX:RHHBY); and against use of Orencia abatacept, a CTLA-4-lg fusion protein from Bristol-Myers Squibb Co. (NYSE:MYO).

As part of the appraisal, the NICE committee recommended against TNF inhibitors Enbrel etanercept from Amgen and Pfizer Inc. (NYSE:PFE), Remicade infliximab from Johnson & Johnson (NYSE:JNJ) and Merck & Co. Inc. (NYSE:MRK), and Humira adalimumab from Abbott Laboratories (NYSE:ABT) to treat RA after the failure of a previous anti-TNF drug (see B9).

Separately, academic researchers published data in the journal of the American Medical Association showing that greater use of erythropoiesis-stimulating agents (ESAs) and iron was associated with a decreased risk of mortality. Amgen markets ESAs Aranesp darbepoietin alfa and Epogen epoetin alfa (see B13).

Biodel Inc. (NASDAQ:BIOD) gained $0.23 to $4.22 last week after FDA accepted for review an NDA for VIAject injectable recombinant human insulin to treat Type I and Type II diabetes.

Celgene Corp. (NASDAQ:CELG) was up $2.39 to $61.91 last week after the U.K.’s NICE issued a final appraisal determination (FAD) against the use of the company’s Vidaza azacitidine in its approved indications, intermediate-2 and high-risk myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMM) and acute myelogenous leukemia (AML) in patients who are not eligible for hematopoietic stem cell transplantation (see Online Links, A26).

Cell Therapeutics Inc. (NASDAQ: CTIC; Milan:CTIC) gained $0.23 (34%) to $0.90 last week and ChemGenex Pharmaceuticals Ltd. (ASX:CGX) was unchanged at A$0.70 after FDA set March 22 for the resubmitted Oncologic Drugs Advisory Committee meeting to discuss NDAs for Pixuvri pexididione from Cell Therapeutics and Omapro omacetaxine from ChemGenex (see B11).

CombinatoRx Inc. (NASDAQ:CRXX) gained $0.37 (33%) to $1.48 on Tuesday after FDA approved Exalgo hydromorphone to manage moderate to severe pain in opioid-tolerant patients. The approval triggers a $40 million milestone from U.S. commercial partner Covidien plc (NYSE:COV). For the week, CombinatoRx gained $0.23 (21%) to $1.35.

Dendreon Corp. (NASDAQ:DNDN) was up $4.07 (13%) to $35.30 last week on two stories. First, despite rumors to the contrary, FDA spokeswoman Shelly Burgess said there will not be an advisory committee meeting to discuss a BLA for Provenge sipuleucel-T.

Separately, Dendreon reported additional data from the Phase III IMPACT trial (D9002B) of Provenge to treat metastatic androgen-independent prostate cancer (AIPC). Provenge continued to extend median overall survival (OS) by 4.1 months vs. placebo after a median follow-up of 36.5 months (see B14).

Human Genome Sciences Inc. (NASDAQ:HGSI) was up $3.63 (13%) to $31.79 last week after the company disclosed in its 4Q09 earnings that FDA accepted for filing a BLA for Zalbin albinferon alfa-2b (formerly Albuteron) to treat chronic HCV.

HGS also reported a 4Q net loss of $0.06 per share; the Street was expecting a net loss of $0.10. In the prior year’s quarter, the company had a net loss of $0.46.

InterMune Inc. (NASDAQ:ITMN) gained $8.67 (59%) to $32.28 last Friday after FDA posted briefing documents ahead of the Pulmonary-Allergy Drugs Advisory Committee meeting on Tuesday this week to discuss an NDA for Esbriet pirfenidone for idiopathic pulmonary fibrosis (IPF). The agency noted that a pooled analysis of two Phase III trials showed a significant improvement in IPF-related mortality (see Online Links, A26).

Earlier in the week, the company submitted an MAA to the European Medicines Agency (EMA) for the p38 mitogen-activated protein kinase inhibitor to treat IPF. InterMune gained $9.54 (69%) on the week.

Isotechnika Pharma Inc. (TSX:ISA) was up C$0.06 (24%) to C$0.32 last week after the European Medicines Agency (EMA) accepted for filing an MAA from Lux Biosciences Inc. for Luneviq voclosporin (LX211) to treat non-infectious uveitis. Lux has rights for ophthalmic indications.

NicOx S.A. (Euronext:COX) gained €0.81 (16%) to €5.98 last week after FDA said it will hold a joint panel meeting on May 12 to discuss an NDA for naproxinod.
to treat osteoarthritis. The PDUFA date is July 24. The cyclooxygenase (COX)-inhibiting nitric oxide donor (CINOD) releases naproxen and nitric oxide.

Separately, NicOx granted Bausch & Lomb Inc. exclusive, worldwide rights to NCX 116 (formerly PF-03187207) to treat glaucoma and ocular hypertension. The biotech will receive $10 million up front and is eligible for up to $169.5 million in milestones, plus double-digit royalties.

Vivus Inc. (NASDAQ:VVUS) was up $0.98 (12%) to $9.38 last week after FDA accepted for filing an NDA for Qnexa phentermine/topiramate to treat obesity.

Clinical milestones

Genzyme Corp. (NASDAQ:GENZ) gained $0.20 to $57.40 last week after it and partner PTC Therapeutics Inc. said ataluren missed the primary endpoint of improvement in a six-minute walk test in a Phase IIb trial to treat Duchenne/Becker muscular dystrophy (DM/BMD) due to nonsense mutation (see B/15).

Ebb & Flow

BioSante Pharmaceuticals Inc. (NASDAQ:BPAX) gained $0.06 to $1.74 last week after the drug delivery, endocrine and genitourinary company raised $18 million through the sale of 10.4 million units at $1.73 in a registered direct offering to Great Point Partners and Deerfield Management (see B22).

Columbia Laboratories Inc. (NASDAQ:CBRX) lost $0.20 (15%) to $1.15 on Thursday after the company said it will sell 11.2 million shares and substantially all of its progesterone assets, including U.S. rights to Crinone progesterone, to Watson Pharmaceuticals Inc. (NYSE:WPI). Columbia lost $0.08 to $1.14 on the week, while Watson was up $0.77 to $40.56 (see B3).

ExonHit Therapeutics S.A. (Euronext:ALEHT) gained €0.30 to €3.49 last week after Allergan Inc. (NYSE:AGN) granted Bristol-Myers Squibb Co. (NYSE:BMY) exclusive, worldwide rights to AGN-209323 (EHT/AGN 0001) and backup compounds outside certain ophthalmic indications.

BMS plans to start Phase II trials in neuropathic pain. AGN-209323 was discovered under a deal between Allergan and ExonHit, which will receive $4 million of Allergan’s $40 million up-front payment and is eligible for about $32 million of Allergan’s $373 million in milestones, plus royalties (see B3).

GeoVax Labs Inc. (OTCBB:GOVX) was off $0.01 (11%) to $0.12 on Monday after the infectious disease company announced plans to raise up to $20 million in a follow-on. The stock was off $0.02 (12%) to $0.12 for the week (see B23).

Neurocrine Biosciences Inc. (NASDAQ:NBIX) was off $0.30 (12%) to $2.30 on Friday after the neurology, endocrine and genitourinary company raised $20 million through the sale of 9.1 million shares at $2.20 in a follow-on. Neurocrine was off $0.32 (12%) for the week (see B22).

Spectral Diagnostics Inc. (TSX:SDI) gained C$0.15 (30%) to C$0.65 last week after the diagnostics company raised C$19.5 million ($18.6 million) through the sale of 48.8 million units at C$0.40 in a previously announced private placement to BioMS Medical Corp. (TSX:MS) and affiliates of GrowthWorks. BioMS was up C$0.03 to C$0.97 (see B22).

XenoPort Inc. (NASDAQ:XNPT) lost $0.57 to $7.42 last week after saying it will reduce headcount by 50%. The company made the move following last month’s complete response letter from FDA for Horizant gabapentin enacarbil, which is partnered with GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), to treat restless legs syndrome (RLS). The partners said FDA indicated that a “preclinical finding of pancreatic acinar cell tumors in rats was of sufficient concern to preclude approval of Horizant for RLS at this time.”

YM BioSciences Inc. (TSX:YM; NYSE-A:YMI) fell C$0.23 (16%) to C$1.70 on Friday and was off $0.25 (18%) to $1.14 on the NYSE-Amex after the cancer company said it plans to raise $17.5 million through the sale of 14.6 million units at $1.20 in a registered direct offering. YM was off C$0.38 (25%) for the week in Toronto and lost $0.34 (23%) on NYSE-A.

— Washington Editor Steve Usdin and Staff Writer Mabel Lam contributed to this week’s Ebb & Flow

Correction

Regulus Therapeutics Inc., Carlsbad, Calif. Business: Infectious, Cancer

Regulus is an independent company. The March 1 BioCentury misstated the company’s status.
Ebb & Flow Focus

Dimebon lost in translation

By Stacy Lawrence
Senior Writer

Dimebon skeptics got the reward they expected last week, as the compound from Medivation Inc. missed the primary and secondary endpoints in the Phase III CONNECTION trial to treat Alzheimer’s disease.

The stock fell $27.15 (67%) to $13.10 on Wednesday after the data were announced, sending the company’s market cap down $910 million to $439 million.

At Feb. 12, short interest in the stock was almost 5.1 million shares — 15% of the 33.5 million shares outstanding. Volume on Wednesday was 4 million, 2.7 times average.

Investors have based their doubts on the compound’s unknown mechanism of action — Medivation believes the oral small molecule enhances mitochondrial function — as well as on the fact that the company’s Phase II trial was run in Russia.

Dimebon latrepirdine has been sold as an antihistamine in Russia for 25 years. Medivation started its Phase II study in September 2005, and reported positive data a year later.

In 2008, Pfizer Inc. paid $250 million up front and committed to paying 60% of development costs for the U.S. rights (see BioCentury, Sept. 8, 2008).

Both CONNECTION and the Phase II trial used the Alzheimer’s Disease Assessment Scale cognitive subscale (ADAS-cog) and Clinician Interview Based Impression of Change plus Caregiver Input (CIBIC-plus) as primary endpoints. The Neuropsychiatric Inventory (NPI), Activities of Daily Living (ADCS-ADL) scale and Mini Mental State Examination (MMSE) were secondary endpoints.

Anna Kazanchyan, managing director of Primary i-Research, which provides custom research to hedge funds, told BioCentury that she’s long had doubts that the Phase II results were replicable.

She noted the trial involved a limited number of research institutions, and that cognitive evaluation endpoints present difficulties in terms of translation and application by Russian physicians, who are unfamiliar with them.

“In the U.S., the Phase II endpoints are standard, but in Russia the use of the same parameters is very limited,” she said. “ADAS-cog is a particularly difficult one to translate. If it’s not something you perform every day, you’re not as good at it. Standardization might have been an issue.”

Placebo responses

Placebo responses differed in the two trials, but wouldn’t have changed the Phase III conclusion, according to Medivation President and CEO David Hung. “A placebo response in the normal range would not have changed the outcome of the CONNECTION study,” he told a conference call.

In CONNECTION, placebo patients remained stable on four of the five endpoints, with significant improvement on MMSE. In the Phase II trial, placebo patients declined significantly across all five endpoints.

CONNECTION included 598 patients across 63 sites in the U.S., Europe and Latin America, with 40% in the U.S. Based on the data, Hung said, “we have to reconsider the entire program.”

Four more Phase III trials of Dimebon are ongoing, three in AD and one in Huntington’s disease. Three are six-month trials, one is a 12-month trial in AD.

Although CONNECTION matched the mean baseline MMSE score of 18 in the first trial, two of the ongoing Phase III studies are in moderate to severe patients. Kazanchyan noted that mild AD sufferers saw the majority of the effect in the Phase II study.

Medivation would not disclose when it expects further data.

Even if Pfizer returns rights to Dimebon, Hung said the pharmaceutical would have to continue to meet its obligations for six months. Pfizer also would have a longer-term commitment to supply the compound, he said.

Medivation’s only other program is MDV3100, a next generation androgen receptor antagonist in Phase III testing to treat castration-resistant prostate cancer. The company has not disclosed when to expect these data.

Data from a Phase III trial reported last year showed a >50% reduction in serum PSA in 45% of chemotherapy-experienced patients and 57% of chemotherapy-naive patients. The trial did not measure overall survival (OS) or progression-free survival (PFS), which are primary and secondary endpoints, respectively, in the Phase III trial.

The prostate program has provided some uplift for Medivation.

The company’s shares rose $3.84 (18%) to $25 in the few days after Johnson & Johnson acquired Cougar Biotechnology Inc. last May for the latter’s abiraterone acetate, which is in Phase III trials to treat metastatic, castration-resistant prostate cancer. Abiraterone is an inhibitor of CYP17.

Following that deal, there was some Street speculation on a deal for MDV3100. Medivation’s shares rose another $1.10 to reach $26.10 just before the company announced in October that it had partnered MDV3100 with Astellas Pharma Inc. in exchange for $110 million up front (see BioCentury, Nov. 2, 2009).

Ascribing those gains entirely to MDV3100 would peg the value of the candidate at $4.94 per share ($165.5 million). The company’s $214.5 million in cash at Sept. 30 would add $6.40 per share, leaving an imputed value of about $380 million.

Medivation ended last week with a $406 million market cap; its shares were down $23.88 (66%) at $12.13.

The biotech reports 4Q earnings on March 15. In the first nine months of 2009, it had an operating loss of $24.8 million.

COMPANIES AND INSTITUTIONS MENTIONED
Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Medivation Inc. (NASDAQ:MDV), San Francisco, Calif.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
At least five biotech and pharma companies reported earnings last week. **Santarus Inc.** (NASDAQ:SNTS) gained 16% after beating the Street’s 4Q09 EPS estimate. Revenues for the quarter, which were up 66% to $62.4 million, were buoyed by a $20 million milestone payment triggered by the approval of Zegerid OTC omeprazole. (A) EPS figure is for FY09 and growth from FY08; Mcap in $M

<table>
<thead>
<tr>
<th>Company</th>
<th>4Q09 EPS est</th>
<th>4Q09 EPS actual</th>
<th>Outcome</th>
<th>Growth from 4Q08</th>
<th>3/5 cis</th>
<th>Wk chg</th>
<th>% chg</th>
<th>Mcap chg</th>
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<tr>
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<td>DKK1.2</td>
<td>NA</td>
<td>88%</td>
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<td>DKK0.95</td>
<td>1%</td>
<td>$34.1</td>
<td>$3,499.0</td>
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4Q09 revenues increased 29% to DKK3.5B ($686M) from DKK2.7B in 4Q08. Sales of Parkinson’s disease (PD) drug Azilect rasagiline increased 33% to DKK225M ($42.6M). In 2009, the company changed its accounting practices for Azilect, resulting in larger recorded sales. The company gave FY10 revenue guidance of DKK14.3-DKK14.8B. Figures include a positive foreign currency exchange impact.

| Ipsen Group (Euromed:IPN) | €1.86 (A) | NA | 7% (A) | 37.07 | - 0.22 | -1% | $25.2 | $4,254.4 |

4Q09 revenues were €255.3M ($367.9M), up 8.2% from €235.9M. Sales for the company’s specialist care business, which includes Apokyn apomorphine and Dysport abobotulinumtoxin A, grew 16% to €157.8M ($227M). Figures include a negative foreign currency exchange impact.

| PDL BioPharma Inc. (NASDAQ:PDL) | $0.19 | $0.17 | Missed by $0.02 | 35% | $7.04 | $0.04 | 1% | $4.8 | $841.3 |

4Q09 revenues fell 15% to $58M from $69M in 4Q08. The prior-year quarter included a $12.5M payment from **Alexion Pharmaceuticals Inc.** (NASDAQ:ALXN) as part of a settlement related to humanized antibodies. PDL expects 1Q10 revenues of $62M.

| Santarus Inc. (NASDAQ:SNTS) | $0.21 | $0.40 | Beat by $0.19 | NA | $4.87 | $0.66 | 16% | $38.4 | $283.3 |

In the prior-year quarter, the company reported a $0.19 loss per share. 4Q09 revenues increased 66% to $62.4M from $37.5M. License and royalty revenue, driven by a $20M milestone payment from **Merck & Co. Inc.** (NYSE:MRK) after FDA approved Zegerid OTC omeprazole, were $23.5M, up from $2.7M. The company gave FY10 revenue guidance of $170-$175M.

| UCB Group (Euronext:UCB) | €1.74 (A) | NA | -6% (A) | 33.30 | 0.80 | 2% | $200.0 | $8,324.0 |

The company did not report quarterly figures. FY09 revenues fell 13% to €3.1B ($4.5B) from €3.6B. Sales of seizure drug Keppra levetiracetam fell 28% to €913M ($1.3B) due to increased pressure from generics. The company gave FY10 revenue and core EPS guidance of €3B and €1.76, respectively.

### Online links this week

**Links to the following documents reside online on the BioCentury Extra page within the Publications section of www.biocentury.com.**

**Alcohol dependence**

CHMP guideline on developing medicinal products to treat alcohol dependence.

**Compassionate access**

Text of the Compassionate Access Act (H.R. 4732), introduced by Rep. Diane Watson (D-N.Y.), which seeks to create a conditional approval system that would allow companies to market new drugs based on Phase I data for life-threatening conditions for which there are no adequate therapies (see BioCentury Extra, Thursday, March 4).

**Crohn’s disease**

NICE final appraisal determination recommending the use of Humira adalimumab from **Abbott Laboratories** (NYSE:ABT) and Remicade infliximab from **Johnson & Johnson** (NYSE:JNJ) and **Merck & Co. Inc.** (NYSE:MRK) to treat severe active Crohn’s disease in patients who have not responded to, who are intolerant of, or have contraindications to conventional therapy (see BioCentury Extra, Friday, March 5).

**EMA**

European Medicines Agency (EMA) revenue and expenditure statement for FY10 (see BioCentury Extra, Thursday, March 4).

**Hematological cancers**

CHMP appendix to the guideline on confirmatory studies in patients with hematological malignancies, and overview of comments received.

**Orphan drugs**

Summary of actions taken at the March 2-3 plenary meeting of COMP, part of the European Medicines Agency (EMA).

**Preclinical trials**

FDA guidance on nonclinical studies evaluating anticancer pharmaceuticals.

**Rheumatoid arthritis**

NICE preliminary appraisal recommending the use of MabThera rituximab from **Roche** (SIX:ROG; NASDAQ:RHHBY) to treat
## Analyst picks & changes

<table>
<thead>
<tr>
<th>Company</th>
<th>Bank</th>
<th>Analyst</th>
<th>Coverage</th>
<th>Opinion</th>
<th>Wk chg</th>
<th>3/5 cls</th>
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</thead>
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<tr>
<td>Actelion Ltd. (SIX:ATLN)</td>
<td>Jefferies</td>
<td>Peter Welford</td>
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<td>Charles Duncan</td>
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<td>Guillaume van Renterghem</td>
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<td>Raghuram Selvaraju</td>
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<tr>
<td></td>
<td></td>
<td>Elemen Piros</td>
<td>Downgrade</td>
<td>Market perform (from market outperform)</td>
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Welford lowered his target to CHF73 from CHF90 after Tracleer bosentan missed the primary endpoint in the Phase III BUILD-3 trial to treat idiopathic pulmonary fibrosis. Welford still rates the stock a buy, saying the company’s pipeline is underappreciated. He expects Phase III data for clazosentan to prevent aneurysmal subarachnoid hemorrhage (aSAH) next half and Phase II data for selexipag to target pulmonary arterial hypertension (PAH) in May. Clazosentan is an endothelin receptor antagonist and selexipag is a long-acting prostacyclin (IP) receptor (PGI2) agonist (see “Actelion Hasn’t Seen Top of PAH,” A7).

Wade also set a $2 target after the company reported 4Q09 sales of Entereg alvimopan of $4.9M, beating his estimate of $4M, and guided to Entereg sales of $30-$35M in 2010. Adolor co-promotes the selective peripherally acting mu opioid receptor antagonist to treat postoperative ileus (POI) in the U.S. with GlaxoSmithKline plc (LSE:GSK; NYSE:GSK).

Duncan lowered his target to $18 from $20 after the company reported a 4Q09 loss per share of $0.22, which missed his and the Street’s loss per share estimates of $0.18 and $0.20, respectively, due to higher than expected operating costs. However, he thinks the increased operating expenses allow the company to ensure a successful launch for Polotyn palatinate. FDA approved the small molecule dihydrofolate reductase (DHFR) inhibitor to treat relapsed or refractory peripheral T cell lymphoma (PTCL) in September 2009.

Yang lowered her target to $36 from $44 after the company reported January sales of Feraheme ferumoxytol of $2.7M, down 61% from $6.8M in December, and said it plans to start two Phase III trials of the compound by mid-year for iron deficiency anemia in patients who have a history of unsatisfactory oral iron therapy or when oral iron cannot be used. Yang lowered her 2010 Feraheme sales estimates to $72M from $74M and increased her 2010 estimated operating expenses to $153M from $137M. The IV iron replacement therapeutic is marketed to treat iron deficiency anemia in adults with chronic kidney disease (CKD).

Duncan downgraded after the company guided to 2010 revenues of $145-$155M, below his and the Street’s estimates of $180M and $171M, respectively, and on its ongoing litigation. Celeria filed suit last month against Health Diagnostic Laboratory Inc. and seven former Celeria employees now employed by Health Diagnostic, alleging the defendants misappropriated trade secrets and engaged in tortious interference with Celeria’s client relationships (see BioCentury, March 1). Duncan also lowered his 2010 and 2011 revenue estimates to $153M and $186M from $180M and $206M, respectively. He lowered his 2011 EPS estimate to $0.04 from $0.08.

van Renterghem also raised his target to DKK92 from DKK70 ahead of Phase III data for zalutumumab to treat head and neck cancer. He believes the data this quarter could lead to an “over-reaction” should it be positive. Zalutumumab is a human mAb against EGFR.

van Renterghem lowered his target to €22 from €27 after Intercell reported lower than expected FY09 results, including €61.7M ($84.1M) in revenues, missing his €91.2M ($124.3M) estimate, and providing “disappointing” limited guidance for 2010. He now expects a loss per share in 2010 and 2011 instead of a profit. He believes Phase II/III data for Intercell’s Staphylococcus aureus vaccine (V710) could be delayed to early 2011 based on the recruitment rate. He also thinks the Phase III trial start for its Pseudomonas aeruginosa vaccine (IC43) in 2H11 suggests a possible launch in 2015 instead of his estimate of 2014. V710 is partnered with Merck & Co. Inc. (NYSE:MRK).

Aschoff lowered his target to $8 from $14 after Medivation announced that Dimebon latrepirdine missed the co-primary endpoints in the Phase III CONNECTION trial to treat Alzheimer’s disease. The oral small molecule that enhances mitochondrial function is partnered with Pfizer Inc. (NYSE:PFZ) (see “Dimebon Lost in Translation,” A23).

Selvaraju downgraded on the Dimebon news.

Piros downgraded on the Dimebon news.
**BioCentury, THE BERNSTEIN REPORT ON BIOBUSINESS**

**March 8, 2010**  
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### Analysts Picks & Changes, from previous page

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<thead>
<tr>
<th>Company</th>
<th>Bank</th>
<th>Analyst</th>
<th>Coverage</th>
<th>Opinion</th>
<th>Wk chg</th>
<th>3/5 cls</th>
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<td>OSI Pharmaceuticals Inc. (NASDAQ:OSIP)</td>
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<td></td>
<td>Canaccord</td>
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<td>Maged Shenouda</td>
<td>Downgrade</td>
<td>Neutral (from buy)</td>
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</table>

Birchough raised his target to $60 from $33 after Astellas Pharma Inc. (Tokyo:4503) began an unsolicited tender offer to acquire OSI for $52 per share, or about $3.5B. He finds the offer at the lower end of bids seen in other biotech acquisitions and expects that a higher bid will ultimately be required (see “OSI’s Last Stand,” A9).

Farmer also raised his target to $55 from $45 on the Astellas news. He thinks the bid price is about right based on Tarceva erlotinib's potential and that a counter-offer is unlikely. His new target includes Tarceva's potential in front-line non-small cell lung cancer (NSCLC). OSI co-markets the small molecule EGFR inhibitor with the Genentech Inc. unit of Roche (SIX:ROG; OTCQX:RHHBY) in the U.S. for second-line NSCLC and pancreatic cancer.

Shenouda also raised his target to $56 from $43 on the Astellas news. He thinks the pharma will need to raise its bid. His new target is based on a survey of recent biotech acquisitions.

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**Online Links, from page A24**

RA after a TNF inhibitor has failed, but against the use of Enbrel etanercept from Amgen Inc. (NASDAQ:AMGN) and Pfizer Inc. (NYSE:PFE); Humira adalimumab from Abbott Laboratories (NYSE:ABT); Orencia abatacept from Bristol-Myers Squibb Co. (NYSE:BMY); and Remicade infliximab from Johnson & Johnson (NYSE:JNJ) and Merck & Co. Inc. (NYSE:MRK) (see BioCentury Extra, Wednesday, March 3).

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**Product documentation**

— Avastin: CHMP refusal assessment report against expanding the label for Avastin bevacizumab to treat glioblastoma after relapse, from Roche (SIX:ROG; OTCQX:RHHBY).

— Esbriet: Briefing documents for the March 9 meeting of FDA’s Pulmonary-Allergy Drugs Advisory Committee to discuss an NDA for Esbriet pirfenidone to treat idiopathic pulmonary fibrosis (IPF), from InterMune Inc. (NASDAQ:ITMN) (see BioCentury Extra, Friday, March 5).

— MabThera: NICE final appraisal determination recommending use of MabThera rituximab in combination with fludarabine and cyclophosphamide to treat relapsed or refractory chronic lymphocytic leukemia (CLL), from Roche (SIX:ROG; OTCQX:RHHBY) (see BioCentury Extra, Thursday, March 4).

— Oleptro: FDA-approved medication guide for Oleptro trazodone to treat major depressive disorder (MDD), from Labopharm Inc. (TSX:DDS; NASDAQ:DDSS).  
— RoActemra: NICE preliminary appraisal recommending against the use of RoActemra tocilizumab to treat moderate to severe rheumatoid arthritis in three settings, while seeking more information on its use in two others, from Roche (SIX:ROG; OTCQX:RHHBY) (see BioCentury Extra, Friday, March 5).

— Vidaza: NICE final appraisal determination recommending against the use of Vidaza azacitidine to treat intermediate-2 and high-risk myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) and acute myelogenous leukemia (AML) in patients who are not eligible for hematopoietic stem cell transplantation, from Celgene Corp. (NASDAQ:CELG) (see BioCentury Extra, Thursday, March 4).

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‘It’s the BioCentury’™
BioCentury 100 Price & Volume Trend

Cumulative weekly performance of 100 biotechnology 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 biotechnology stocks listed on the LSE or AIM, 12-week period. Index base =1000 on May 10, 1996.

Thomson Reuters Life Sciences Indexes

Weekly change in combined market capitalization. 12-week period. Tier 1 = market cap>$1B; Tier 2 <$1B. Base =100 on Dec. 31, 1998.

Price Gains

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

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<th>Company</th>
<th>Ticker</th>
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<th>$Chg</th>
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<th>Vol(00)</th>
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Price Declines

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

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<th>$Chg</th>
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Volume Gains

Greatest changes in volume above 5,000 shares.

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<td>OSI</td>
<td>OSIP</td>
<td>621740</td>
<td>950%</td>
<td>56.990</td>
<td>19.970</td>
</tr>
<tr>
<td>NicOx</td>
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<td>52733</td>
<td>744%</td>
<td>€5.98</td>
<td>€0.81</td>
</tr>
<tr>
<td>Resverlogix</td>
<td>RVX</td>
<td>27275</td>
<td>683%</td>
<td>€5.02</td>
<td>€2.86</td>
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<tr>
<td>Epistem</td>
<td>EHP</td>
<td>276</td>
<td>656%</td>
<td>€3.25</td>
<td>2.5p</td>
</tr>
<tr>
<td>InterMune</td>
<td>ITMN</td>
<td>417821</td>
<td>512%</td>
<td>23.280</td>
<td>9.540</td>
</tr>
<tr>
<td>Transition Therap</td>
<td>TTHI</td>
<td>13037</td>
<td>481%</td>
<td>2.683</td>
<td>0.043</td>
</tr>
<tr>
<td>Neurocrine</td>
<td>NBIX</td>
<td>44178</td>
<td>478%</td>
<td>2.300</td>
<td>-0.320</td>
</tr>
<tr>
<td>Abcam</td>
<td>ABC</td>
<td>3432</td>
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<td>1056p</td>
<td>15p</td>
</tr>
<tr>
<td>Questcor</td>
<td>QCOR</td>
<td>93143</td>
<td>395%</td>
<td>6.500</td>
<td>1.820</td>
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Volume Declines

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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>Hutchison China</td>
<td>HCM</td>
<td>27304</td>
<td>-11%</td>
<td>218.8p</td>
<td>15.8p</td>
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<tr>
<td>Penwest</td>
<td>PPCO</td>
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<tr>
<td>Medivation</td>
<td>MDVN</td>
<td>69388</td>
<td>-23%</td>
<td>12.130</td>
<td>€23.880</td>
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<tr>
<td>Mologen</td>
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<tr>
<td>OSI</td>
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<td>52733</td>
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<td>€5.98</td>
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<td>27275</td>
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</tbody>
</table>

1 Volume figure is of ADSs (ADS = 8 shares)
2 Includes volume from TSX

Source: Thomson Reuters

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Chimerix Inc.
Complete Genomics Inc.
Cytori Therapeutics Inc. (NASDAQ:CYTX; Xetra:XMPA)
Depomed Inc. (NASDAQ:DEPO)
Dyax Corp. (NASDAQ:DYAX)
Enobia Pharma Inc.
Exact Sciences Corp. (NASDAQ:EXAS)
Facet Biotech Corp. (NASDAQ:FACT)
Five Prime Therapeutics Inc.
Gemin X Pharmaceuticals Inc.
GlobelImmune Inc.
Inovio Biomedical Corp. (NYSE-A:INO)
iPierian Inc.
KaloBios Pharmaceuticals Inc.
Lux Biosciences Inc.
Medivation Inc. (NASDAQ:MDVN)
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Neoprobe Corp. (OTCBB:NEOP)
NeurogesX Inc. (NASDAQ:NGSX)
Newron Pharmaceuticals S.p.A. (SIX:NWRN)
PDL BioPharma Inc. (NASDAQ:PDLI)
Pharming Group N.V. (Euronext:PHARM)
Plexxikon Inc.
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RXi Pharmaceuticals Corp. (NASDAQ:RXII)
Seaside Therapeutics LLC
Singulex Inc.
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