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Main Offices

PO Box 1246,
San Carlos CA 94070-1246
650-595-5333; Fax: 650-595-5589

www.biocentury.com

Chicago: 312-755-0798; Fax: 312-755-0658
Washington D.C.: 202-462-9582; Fax: 202-667-2922

BioCentury International

Oxford, UK: +44 (0)1865-512155; Fax: +44 (0)1865-311195

Corporate

Karen Bernstein, Ph.D. Chairman & Editor-in-Chief
David Flores President & CEO

Executive Administrator: Kris Hall

Eric Pierce, Tim Tulloch Associate Publishers
Bennet Weintraub Finance Director

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Product Development**COX-2s on the brain**

**By Christopher Maggos
Senior Writer**

Affectis Pharmaceuticals AG thinks certain COX-2 inhibitors could be efficacious in depression and schizophrenia and has recent clinical studies by academics and internal preclinical research to support its hypotheses. Last week, the company in-licensed Palau Pharma S.A.'s cimicoxib, which had completed some Phase II testing for pain.

**This week's briefing**

*Affectis: COX-2s
on the brain*

...

*Millennium: Expanding
Velcade sales*

"Depression and schizophrenia are inflammatory diseases," Affectis CEO Herbert Stadler said. "This is an observation that dates back to before the second World War, but in the last 10-20 years, several biochemical markers have supported the theory."

Increased levels of pro-inflammatory cytokines and prostaglandin E (PGE) have repeatedly been described in major depression, researchers from Ludwig Maximilians University in Munich wrote in a 2006 *Molecular Psychiatry* paper. COX-2 inhibitors inhibit production of both. In addition, Stadler noted, COX-2 is expressed in regions of the brain that

are implicated in depression.

The Ludwig Maximilians researchers reported in the same publication that Celebrex celecoxib was better than placebo when used in combination with SSRIs in a double-blind trial in 40 patients suffering from an acute depressive episode.

Stadler told BioCentury that a number of coxibs — those that passed the blood-brain barrier — worked in an animal model of depression.

The company didn't see similar antidepressant effects when it tested non-selective NSAIDs. "The old NSAID compounds have limited COX-2 activities and blood-brain barrier penetration," Stadler noted.

The mechanism by which some COX-2 inhibitors work in depression could be linked to their anti-inflammatory mechanisms, but there also is some evidence in the literature that COX-2 is linked to memory processing and memory storage, Stadler said. "Memory processing decides whether you classify something as a negative experience or a positive experience. If you file too much of what happens to you during a day as negative then you end up depressed."

Although Affectis found that monotherapy with coxibs worked just as well as SSRIs in its mouse models, the company is planning to pursue development of cimicoxib as an add-on therapy during the first six weeks of treatment with antidepressants, Stadler said, noting that SSRIs take about that long to start working. The preclinical and clinical studies of existing coxibs showed efficacy during the first six weeks.

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Expanding Velcade sales

To grow sales of its key drug, Velcade bortezomib, Millennium Pharmaceuticals Inc. is taking a multi-pronged approach that includes earlier use of the proteasome inhibitor in its approved indication of multiple myeloma, getting doctors to prescribe more cycles of the drug in its approved indications, and adding new indications in larger cancer markets.

Velcade already has a foothold in the first-line setting for MM, as the company has estimated that off-label use suggests 10% penetration. The company is hoping Velcade combinations lead to a label expansion in first-line disease. The foundation for Velcade's growth "is a significant survival advantage on its own," said President and CEO Deborah Dunsire. "It's also a powerful combination agent."

The company is running three Phase III combination trials: VISTA, IFM and HOVON. Last month, the company reported preliminary data from IFM that showed a complete/near complete response rate of 20% for Velcade plus dexamethasone vs. 9% for the combination of vincristine, adriamycin and dexamethasone (VAD).

VISTA is testing Velcade plus melphalan and prednisone vs. melphalan and prednisone alone, while the treatment arm of the HOVON study is looking at Velcade plus doxorubicin and dexamethasone (PAD) therapy before stem cell transplant, followed by maintenance therapy with Velcade. The control arm is vincristine plus adriamycin and dexamethasone (VAD) as induction therapy prior to transplant, followed by thalidomide maintenance. MLNM has not provided guidance on when it hopes to have data from those two studies.

In the second arm of the strategy, the company recommends that patients receive 8 cycles of therapy in Velcade's approved indications of second line MM and mantle cell lymphoma, which was the number used in late-stage trials of the drug. Currently, patients average about 6 cycles, which is up from 5.5 cycles in early 2006.

As to broader indications, MLNM is running a Phase III trial of Velcade plus Rituxan rituximab from Biogen Idec (BIIB) and Genentech (DNA) in relapsed follicular NHL. MLNM said that market includes about 35,000 patients in the U.S. — *Steve Edelson*

(A) Used mid-point of MLNM's FY07 guidance of \$240-\$260M; (B) Disclosed in 2Q06 earnings; NA = Not available

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The company may not pursue chronic use because of safety concerns, he said. "We think this is still a very good market as an add-on therapy. The cardiovascular risk from COX-2s during the first six weeks, I think everyone would agree, is low."

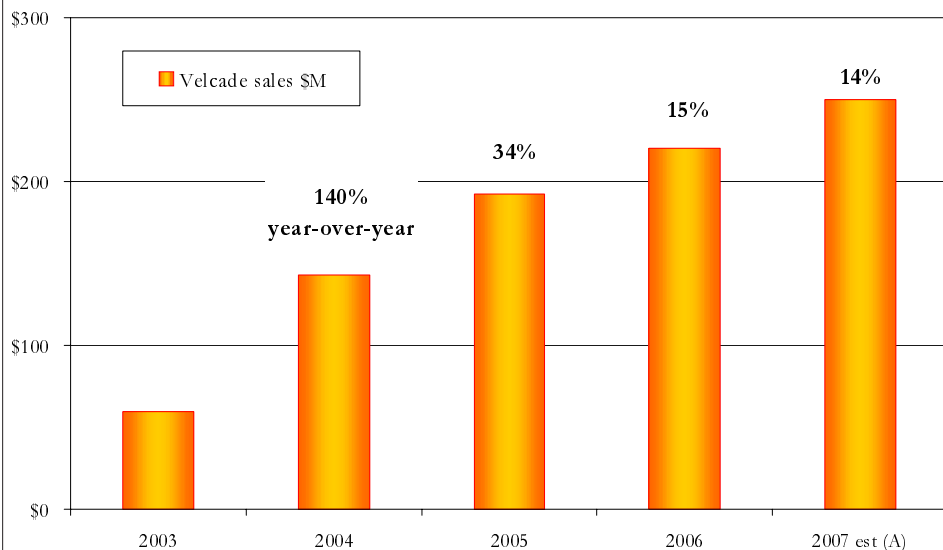
A Phase IIa trial of cimicoxib in depression is slated to start in the second quarter.

Affectis also may develop cimicoxib in schizophrenia based on a positive double-blind academic study of Celebrex or placebo plus marketed therapy published in 2002 by the same group at Ludwig Maximillians in the *American Journal of Psychiatry*. Affectis will make a decision after it sees results from an ongoing Phase II study in Munich. If the results are good, the company plans to start a Phase IIa trial in 2008.

Under the deal, Palau (Barcelona, Spain) granted Affectis (Munich, Germany) an exclusive worldwide license to cimicoxib for all CNS indications, excluding pain (see B2).

Affectis also has an internally discovered partial agonist of P2X7 calcium channels in preclinical development for depression. "With luck, we might enter Phase I by year end in depression," Stadler said.

Affectis raised €12 million (\$15.1 million) in a series C round in October (see *BioCentury*, Oct. 30, 2006).



Indication (Status)	U.S. patients	Cost/cycle (No. of cycles)	Total cost per patient	Estimated penetration
2nd line MM (2003 FDA approval)	25,000	\$4,523 (6)	\$27,137	55%(B)
Mantle cell lymphoma (2006 FDA approval)	5-6,000	\$4,523 (6)	\$27,137	NA
1st line MM (Ph III)	25,000	\$4,523 (4)	\$18,091	10% (off-label)(B)
Relapsed follicular NHL (Ph III)	35,000	\$4,523 (NA)	NA	NA

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