

# BioCentury

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## Strategy

# Nektar's next step

By Michael Flanagan  
Senior Writer

**Nektar Therapeutics** had expected to become profitable in mid-2007 based on royalties from Exubera inhaled insulin. Instead, partner **Pfizer Inc.** terminated the diabetes drug from its portfolio that October because it failed to gain acceptance from patients and physicians.

But even before Exubera imploded, Nektar had begun to change its focus from the formulation deals that had been its bread and butter, to developing its own products (see *BioCentury*, Feb. 6, 2006). Last week, the company announced progress along that path in the form of a deal with **AstraZeneca plc** for its lead program.

AstraZeneca will pay \$125 million up front for worldwide rights to NKTR-118, a pegylated form of the opioid antagonist naloxol that is in Phase II trials treat opioid-induced constipation (OIC). The pharma also gets rights to NKTR-119, a preclinical program combining NKTR-118 with an opioid to treat pain without causing constipation.

Nektar is eligible for up to \$610 million in milestones for NKTR-118 and \$385 million in milestones on each of the first two compounds from the NKTR-119 program, as well as tiered, double-digit royalties on both.

"When Pfizer took Exubera off the market, that could have been a death blow for Nektar," said President and CEO Howard Robin, who was hired in 2007 to accelerate the company's transition to drug development (see *BioCentury*, Aug. 27, 2007).

Indeed, it had become "apparent that Nektar's principle business of engineering inhaled products for partners was no longer viable," he said. "The number of opportunities available for delivering drugs to the lungs or systemically via the lungs are somewhat limited, and you cannot readily build value based on the relatively low royalties from inhaled programs."

Nektar sold most of its pulmonary drug delivery business to **Novartis AG** last year for \$115 million in cash.

Meanwhile, Robin has overseen multiple restructurings that have reduced headcount from 1,200 employees to 350, which he said has reduced annual burn by \$100 million. The company also created a clinical development team for the first time.

NKTR-118 was created using Nektar's advanced polymer conjugate technology, which emerged from its expertise in pegylation of large molecules (see *BioCentury*, Sept. 24, 2007).

Nektar had conducted some early Phase I work with NKTR-118 in volunteers prior to Robin's arrival. With a dedicated clinical development team now in place, the company moved into a Phase II trial in early 2008.

"We saw the potential in this program given the estimated 230 million scrips written each year for opioids and the fact the literature suggests that between 50% and 90% of patients on opioids will become severely constipated because one side effect of the drugs is to paralyze the bowel," Robin said.

The company believes NKTR-118 should antagonize opioid  
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Howard Robin, Nektar Therapeutics

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receptors in the gut while avoiding any impact on analgesia because its pegylation prevents it from crossing the blood-brain barrier.

In March, the company reported top line Phase II results showing 25 and 50 mg of oral NKTR-118 given once daily met the primary endpoint of significantly increased spontaneous bowel movements from baseline after one week vs. placebo ( $p < 0.01$  for each). “Importantly,” said Robin, “there was no loss of analgesic benefit” as measured by a change in pain Numerical Rating Scale and no increase in opiate use, added Robin.

“The challenge has been taking a relatively large PEG structure and applying it to a small molecule in a way that doesn’t break the activity of the small molecule,” Robin said.

Drawing on its experience with pegylating large molecules, Nektar has found ways to modify the solubility of linkers and for using multi-arm architectures employing a central PEG molecule with an active small molecule on each arm.

“There are hundreds of small molecule drugs that we could apply the technology to and improve the pharmacokinetic and pharmacodynamic profiles,” while also making them orally bioavailable, Robin said.

Nektar’s next most advanced internal program is NKTR-102, a pegylated irinotecan in Phase II testing for a number of cancers, with platinum-resistant ovarian cancer as the lead indication. NKTR-105, a pegylated docetaxel, is in Phase I testing for solid tumors.

Robin hopes to reach the point soon where Nektar is churning out 2-3 INDs per year, and believes the company will ultimately reach the point where it will be interested in doing its own Phase III testing and possibly commercialization.

“We need to first feel like we have sufficiently explored the polymer conjugate technology to say what type of molecule and therapeutic area it is best served by while also being at a point where we can afford both the successes and failures of Phase III drug development,” he noted.

The deal with Novartis did not include a pair of pulmonary drug delivery programs partnered with **Bayer AG**: NKTR-061 (BAY41-6551): an inhaled amikacin expected to begin Phase III testing this year for hospital-acquired, Gram-negative pneumonia, and ciprofloxacin inhaled powder (CIP), a 4-quinolone antibiotic in Phase II testing to treat chronic lung infections in cystic fibrosis (CF) patients.

At June 30, Nektar had \$294.3 million in cash and a six-month operating loss of \$60.8 million.

#### COMPANIES AND INSTITUTIONS MENTIONED

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

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

**Nektar Therapeutics** (NASDAQ:NKTR), San Carlos, Calif.

**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland

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