

## **WINNER BY A NOSE?** Profile, Nastech Pharmaceutical

The company hit the headlines in early March with promising results from an early-stage trial of a nasal spray to treat obesity – as well as positive results from a second-stage trial of a nasal spray to treat erectile dysfunction.

It is a leader in drug-delivery technologies, specifically formulations of difficult-to-deliver injectable and oral drugs that can be administered nasally.

**Nastech Pharmaceutical Co.** (Dr. Steven Quay, chmn., pres. & CEO), Bothell, Wash., was started in 1983 to reformulate generic drugs that would benefit from nasal rather than oral delivery. Drugs delivered nasally act quickly – within seconds – and can be more effective and have fewer side effects than pills or injections.

Nastech's strategic direction changed in mid-2000 when the board hired Quay – who had come into contact with Nastech as a supplier of an intranasal agent for use in a diagnostic protocol – after the previous CEO's death.

Quay – who had run three different medical-related businesses, including Bothell-based **Sonus Pharmaceuticals** – shifted the development focus away from generics to proprietary drugs. Quay set sights high, targeting markets with potential annual sales of at least \$1-billion.

In 2002, Quay moved Nastech's headquarters and most of its research-and-development work from Hauppauge, N.Y., to Bothell for proximity to the growing cadre of entrepreneurial biotechnology companies in the Seattle area.

The key to the Nastech story, in the words of an outsider: “If you have a non-invasive form of a drug that you'd otherwise have to take by injection, you have a huge advantage. It's that simple.”

Nastech seeks to develop nasal formulations of difficult-to-deliver compounds, to protect its work by patents, to conduct early-stage clinical trials where necessary and then to partner with big pharmaceutical companies.

The development portfolio now includes products targeting (among others) sexual dysfunction, obesity, pain management, osteoporosis and multiple sclerosis.

Nastech's research focuses on “tight junctions” – pathways between cells through which molecules of various sizes may or may not pass depending on circumstances. Tight junctions of special interest in drug delivery are found in nasal tissue, intestinal tissue, in blood vessels generally and especially in blood vessels in the brain.

The larger its molecular weight, the tougher it is for a drug to pass through a tight junction. Nastech aims to understand the structure and function of these barriers and to identify compounds that can open them. It has genetically engineered and produced many key proteins in tight junctions and uses them as targets to identify peptides and small molecules – tight-junction modulators – that can improve drug delivery by temporarily opening junctions. Popping a pill is the most common and cheapest way to take a drug. But gastrointestinal and liver metabolism can reduce an oral drug's effectiveness. Injections can be uncomfortable and obviously are invasive.

Nastech's list of the benefits of nasal delivery include faster action, lower doses, fewer side effects, greater safety and efficacy, greater convenience and compliance and, potentially, lower costs.

Beyond nasal drug delivery, Nastech research on tight junctions has significant potential applications for manipulating other tissue barriers and improving other routes of drug

delivery, including pills and injections.

Most of the recent excitement at Natestch – including a new high in its stock – arises from positive developments on two fronts announced by Natestch on March 10.

¶ An early (and small) trial of an intranasal formulation of a product called PYY 3-36 showed a significant reduction in appetite and calorie intake both immediately after administration and for up to 24 hours. A Natestch officer describes PYY as “a natural hormone produced by the gut after a meal in proportion to the caloric intake” that is believed to signal satiety to the brain.

¶ Another trial, of intranasal apomorphine for erectile dysfunction, “demonstrated excellent efficacy, was well tolerated with minimal side effects, and had an onset of action about 15 minutes after dosing.” This is a potential competitor to drugs such as Viagra, Cialis and Levitra.

In the PYY study, nine of 11 healthy overweight men and women administered a single dose via nasal spray an hour before lunch showed a mean reduction of 8.2% in caloric intake vs. placebo, and five of the 11 had a calorie reduction of 24% or greater.

Over the 24-hour period following administration of that single dose, the mean caloric reduction in “a setting of boundless, attractive food choices” was 4%, with four of the subjects showing a reduction of 15% or more. A Natestch officer told analysts in a conference call, “We’re encouraged by the results: appetite reduction, calorie reduction even without dietary changes, and a well-tolerated safety profile.” A study begun in February aims to determine the optimal dosing sequence for satiety and calorie reduction and is expected to be the final step before phase II trials. Natestch notes that Americans now spend \$33-billion a year on weight-loss products and services.

The erectile-dysfunction compound, apomorphine, dates from the 19th century and has been successfully used to treat Parkinson’s disease. An oral formulation for sexual dysfunction called Uprima is sold in Europe, but side effects keep that drug off the market in the U.S.

Natestch says that in Phase II trials it has found a dose “that is safe and well tolerated that is significantly above doses demonstrated in prior studies to produce efficacy” – yet contains only an eighth of the active ingredient as the European oral drug.

An apomorphine partnership ended last year when the Federal Trade Commission – fearing **Pharmacia & Upjohn’s** merger with Viagra-maker **Pfizer** would inhibit competition – forced Pharmacia to divest all rights to intranasal apomorphine. Besides reacquiring rights, Natestch received \$13.5-million from Pharmacia.

Natestch will seek a new commercialization partner for an apomorphine nasal spray before initiating pivotal phase III trials. Analysts think the drug could reach the market by late 2006. Worldwide sales of erectile-dysfunction drugs exceed \$1-billion a year and are rising.

In late 2003, Natestch filed an abbreviated new drug application for the first generic version of intranasal salmon calcitonin to treat osteoporosis. Salmon calcitonin works much longer in the bloodstream than human calcitonin.

A salmon-calcitonin product from **Novartis** to prevent bone loss in menopausal women, Miacalcin Nasal Spray, generates \$400-million annually. The Natestch generic could enter the U.S. market late next year. Natestch notes the osteoporosis-pharmaceutical market is expected to double from the current \$7-billion by 2011.

Natestch sees “near-term commercialization opportunities” on three other programs: nasal formulations of interferon beta for multiple sclerosis and of morphine gluconate for

breakthrough pain in chronic pain patients, and an orally administered long-acting opioid for pain called CC-109 that does not have the abuse potential of OxyContin.

Unlike OxyContin, CC-109 tablets do not release the active opioid oxycodone when they are crushed and thus cannot be snorted or injected for an immediate high. Annual sales exceed \$1.1-billion for injectable interferon beta and \$5.6-billion for all narcotic painkillers (up 127% since 1999), including \$1.9-billion in OxyContin sales.

Other previously disclosed development programs include nasal formulations of interferon alpha to fight cancer and treat chronic hepatitis, somatotropin for human-growth-hormone deficiency, and triptans for migraine-pain relief. Analysts at **W.R. Hambrecht + Co.**, New York, believe Nastech is working on “at least 10 biological developments either on a disclosed or undisclosed basis.”

Nastech last year sold for \$14-million plus \$4-million in contingent payments its Nascobal brand of intranasal formulations of vitamin B-12 to **Questcor Pharmaceuticals Inc.** because the limited market opportunity for vitamin B-12 deficiency did not fit its overall strategic plan.

It also sold to **Cytec Corp.** patent rights for a breast-pump-like device developed by Quay in the mid-1990s and already approved by the FDA to test for early signs of breast cancer. Nastech received a license fee and will receive milestone payments and royalties for a test that may eventually become as ubiquitous as the pap smear.

Nastech stock (NASDAQ symbol NSTK; \$12.23 March 29) has nearly doubled from the low of \$7.06 a year ago – rising roughly 77% between mid-December and mid-March to a high of \$14.65. Since then it has pulled back about 17%. Market capitalization is tiny, only about \$150-million. Shares outstanding total 11.83-million, with a float of 8.9-million. Average daily volume is about 90,000 shares. Insiders own nearly 25%, institutions about 21%.

Hambrecht – which has a “buy” rating on Nastech stock, with a 12-to-18-month target of \$22.20 and a “terminal valuation” of \$37 in 2007 – sees the company turning profitable in fourth-quarter 2006 based on earnings derived from commercialization of generic salmon calcitonin in 2005 and apomorphine in 2006.

Nastech’s accumulated deficit totaled \$54.8-million at yearend 2003. The company has financed itself by selling stock and via research revenue. Hambrecht now projects that Nastech will experience additional net losses totaling \$60-million in the three years from 2004 through 2006, then earn \$11.5-million, or 95 cents a share, in 2007.

These estimates assume Nastech will license both its intranasal apomorphine and interferon beta programs – with each yielding \$50-million in licensing fees spread over the clinical development phase and the first years of marketing, coupled with a sales-based royalty of 15-20%.

Is this a stock you want to own? A company with innovative drugs to treat obesity and erectile dysfunction is an attention-grabber, for sure. But veteran biotech investors know the warning label on the merchandise: Great early-stage research carries no guarantee of commercialization.

A Hambrecht + Co. analyst says: “Nastech has developed intranasal delivery technology more comprehensively than any other entity [and its] ability to develop intranasal formulations of biological drugs [is] an important accomplishment that sets it apart. During the current decade, development of biological drugs will increase significantly. Nastech is poised to benefit as one of a few companies offering a formatting alternative beyond the use of needles and syringes.”\_