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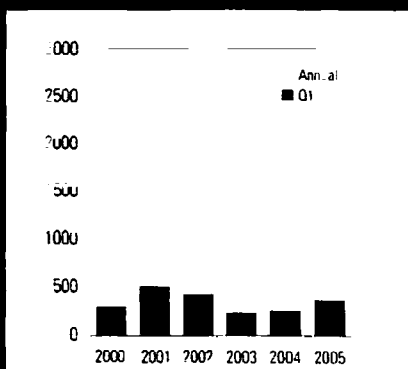
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Venture Abroad

Small surges in biopharmaceutical and medical-investing helped elevate the first quarter fund raising in Europe. See sector-by-sector breakdowns in this month's Sector Watch.



Source: VentureSource

VCs Show More Interest In Funding Phase III Trials Themselves

BY TOM SALEMI

Venture capitalists once looked upon pharmaceutical companies and public investors as partners in the effort to get drugs on the market. Today, however, venture capitalists are beginning to see the value in going it alone.

In a trend illustrated by the \$163 million pumped into Somaxon Pharmaceuticals Inc. and Verus Pharmaceuticals Inc., venture capitalists are showing they can muster the capital and means to support companies attempting to get products through Phase III clinical trials or onto the market.

The financings demonstrate how venture capital firms with large funds can use their muscle to compensate for weak public markets while going forward without agreeing to overly aggressive demands from corporate partners. "Obviously everything is a case-by-case instance," says Jesse Treu, general partner at Domain Associates, which is an investor in both companies. "But I would not be surprised to see more and more boards thinking very hard about partners and when to partner."

In doing so, venture capitalists are working from a position of strength

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Once Neglected, Gastrointestinal Diseases Begin To Draw Biotech Investors

BY BRIAN GORMLEY

When biotech investors talk about large markets they're more likely to speak of diabetes or depression than gastrointestinal disorders, even though maladies such as irritable bowel syndrome affect about as many Americans as these two conditions combined.

VCs have avoided markets such as irritable bowel syndrome—which affects 36 million in the United States—because the disorders traditionally have been difficult to diagnose and even harder to treat.

But with understanding of these conditions improving, more firms are moving in. Forward Ventures, for example, made its first gastrointestinal deal last month, spinning an irritable bowel syndrome compound out of Merck KGaA to create Tioga Pharmaceuticals. In May, Thomas, McNerney & Partners, HIG Ventures and Quaker BioVentures led a \$32

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IBS in the U.S. and Europe seek treatment.

That's still a large opportunity, however, and one that is growing because of the efforts of GlaxoSmithKline and Novartis, whose marketing of Lotronex and Zelnorm respectively, have helped educate doctors as well as patients. But both drugs have limitations. Lotronex, approved only for women with severe diarrhea-predominant IBS on whom other treatments failed, comes with a warning about ischemic colitis, in which blood flow is reduced to the intestines. Last year, the FDA updated the labeling of Zelnorm—used for short-term treatment of constipation-predominant IBS in women—to include risk information about ischemic colitis and serious consequences of diarrhea that have been linked to the drug.

Yet Mr. Collinson and others point to the success of Zelnorm in particular as a sign of how valuable a better IBS therapy might be. The drug, approved in the United States in 2002, drew \$249 million last year and analysts estimate that sales could top \$550 million in 2006.

One approach is to apply compounds that have been studied in central nervous system diseases to IBS. The gastrointestinal tract, as it turns out, has as many neurons as the spinal cord, and most of the neurotransmitters in the brain also work there to regulate the movement of food and other processes. Antidepressants, in fact, have long been used off label for the disorder.

This strategy builds on the success of Lotronex and Zelnorm, which target receptors for the neurotransmitter serotonin. Lotronex relieves diarrhea by blocking the serotonin receptor 5-HT₃, for example.

Dynogen Pharmaceuticals, Waltham, Mass., was formed in 2002 to capitalize on its founders' expertise in the neurological basis of gastrointestinal disorders. It acquires CNS compounds that have been studied in humans and tests them in various animal models of gastrointestinal diseases, such as in rats, cats and dogs, before bringing them forward. Vice President Mark F. Boshar described the animal testing as more thorough than that of other gastrointestinal-drug companies.

Its first IBS product, for the diarrhea-predominant version, blocks the 5-HT₃ receptor to treat diarrhea and inhibits noradrenalin reuptake to reduce pain. But the compound, licensed from Mitsubishi Pharma—which tested it in Phase II for Alzheimer's and depression—does not have the side effects of tricyclic antidepressants, noradrenalin-modifying drugs used off-label for IBS, according to Dr. Ted T. Ashburn, senior director of business development.

The company, which has raised \$63 million from SV Life Sciences, Oxford Bioscience Partners and others, is testing the product in early human trials but declined to disclose the precise clinical stage.

Vela Pharmaceuticals, Ewing, N.J., also is developing an IBS molecule that works in multiple ways. The compound is derived from a drug used in Japan, Korea and Central Europe to treat conditions ranging from bowel disturbances—including IBS—to menopausal hot flashes.

Vela contends that the drug works for all these conditions because it affects the hypothalamus, part of the brain that regulates body temperature and a range of involuntary processes, including those in the gut. The compound seems to have anti-inflammatory properties as well.

The combined effect appears to be potent. In a Phase II study of 141 participants, those in the treated group said they got adequate relief 57 percent of the time over a three-month span, compared with the placebo group that reported relief 43 percent of the time. In some the difference was dramatic. A woman who was having 20 bowel movements a day got down to five or six, said CEO Kevin L. Keim.

Unlike Lotronex, Vela's product could be taken by men as well as women. More important, it caused constipation just 2 percent of the time, compared with 29 percent in studies of Lotronex.

Vela, backed with \$44 million from JPMorgan Partners, Venrock Associates, New Enterprise Associates and others, is preparing for a Phase II-b that would test the therapy at different doses and in a larger group. The company also is developing a product for depression in Phase II.

Small companies like Vela and Dynogen will likely need a pharmaceutical company to finance Phase III studies, which will require up to 3,000 subjects. Copenhagen-based Gastrotech Pharma has found such a partner in Eli Lilly. The companies are testing a derivative of glucagon-like peptide-1 in Phase II-b that normalizes gut contractility to relieve pain. The product, injected subcutaneously, may ease other IBS symptoms as well, said Florian Schonharting, a partner of Nordic Biotech, the Danish firm which spun Gastrotech out of Gothenburg University two years ago.

Tioga Pharmaceuticals, San Diego, attacks IBS pain differently. The molecule it acquired from Merck KGaA targets kappa receptors in the gut, an approach that could reduce discomfort without constipation and other side effects of painkillers, such as morphine, that bind to mu receptors.

Merck KGaA, which saw promising results from Phase II studies in women and men with diarrhea- and constipation-predominant IBS, divested the product so it could concentrate on cardiovascular disease and cancer, said Forward Ventures' Mr. Collinson, Tioga's acting CEO. The company soon expects to move the compound into Phase II-b.

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FROM THE FRONT

Gastrointestinal Diseases

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Not everyone sees IBS as the ideal first target. Tranzyme Pharma, Research Triangle Park, N.C., is initially targeting post-operative ileus, which it could reach on its own with a small hospital-based sales team.

Patients emerging from abdominal surgery often have impaired bowel function. Though the reason is unclear, scientists say opioids and natural endorphins contribute to the problem, which forces hospitals to keep patients until they have had their first bowel movement.

Publicly held Adolor and Progenics Pharmaceuticals are developing drugs that block the effects of opioids in the gut but not in the brain, reducing the gastrointestinal side effects without interfering with analgesia.

Tranzyme's tack is more direct. Its lead product induces the movement of food through the digestive tract by activating a receptor for ghrelin, a peptide that stimulates gastric motility. But the compound differs from natural ghrelin in that it induces motility without prompting the release of growth hormone, which would be undesirable, said CEO Vipin K. Garg. The company aims to file for permission to begin clinical trials by year-end.

To drive adoption, Tranzyme, Adolor and Progenics must show that their products get patients out of the hospital sooner. In a Phase II, the Progenics compound shortened stays by 24 hours. If these results hold up in Phase III the molecule could reach the high end of its \$600 million to \$800 million market potential, said Kevin DeGeeter, an analyst with Dawson James Securities. Adolor has filed its new drug application. But the European Phase III, in which the product did not achieve statistical significance in its primary endpoint of time to gastrointestinal recovery, may hurt its chances of gaining approval.

In any case, Tranzyme won't need to displace these products because its approach is complementary, its backers said. Tranzyme, which has raised \$42 million, has earlier-stage products for larger conditions such as diabetic gastroparesis—a bowel impairment—and diarrhea-predominant IBS.

While corporations have dominated IBS, small companies are beginning to make inroads elsewhere. Santarus, a specialty pharmaceutical company focused initially on gastroesophageal reflux disease, in which stomach acid backs up into the esophagus, held a \$54 million IPO last April and completed a \$66 million follow-on offering last July. It had drawn \$95 million in venture capital from St. Paul Venture Capital, Domain Associates, Advent Venture Partners and

JPMorgan, among others.

Santarus sells a fast-acting version of the proton-pump inhibitor omeprazole, which blocks stomach acid production. Unlike proton-pump inhibitors such as AstraZeneca's Nexium, which are absorbed in the small intestine, Santarus' drugs are absorbed into the bloodstream through the stomach. The company sells an oral-suspension version and has filed for approval for capsule and chewable tablet forms as well. It hopes both will gain clearance by late March.

The capsule is particularly important because it is the version patients are most familiar with. Investors are therefore waiting to see how successful Santarus will be in driving its adoption in the market for proton-pump inhibitors, which is worth \$12.5 billion in the United States and growing at 7 percent a year. St. Paul, JPMorgan, Domain and Advent have retained their stakes, according to Santarus' most recent proxy statement.

"We're in a very competitive, very noisy marketplace," said CEO Gerald T. Proehl. To distinguish itself, Santarus will have to sell doctors on the benefits of its faster-acting product.

A few venture-backed companies are targeting inflammatory diseases of the gut, such as ulcerative colitis and Crohn's disease. They include **Androclus Therapeutics**, San Diego, and **ChemoCentryx**, Mountain View, Calif., which are developing better means of controlling the inflammation that damages the gastrointestinal tract. (For more about these and other companies targeting inflammatory diseases, see the biopharmaceutical Sector Watch on page 8.)

Not all investors are comfortable targeting conditions like Crohn's or IBS that are not well understood. Warburg Pincus, U.S. Venture Partners and others hope they've found a less-risky play in Cambridge, Mass., based **Altus Pharmaceuticals**. The company's most advanced product, **TheraClec**, which recently completed Phase II, replaces three digestive enzymes that are deficient in people with pancreatic insufficiency, which affects those with cystic fibrosis, pancreatic cancer and other diseases. The product met its primary endpoint of improved fat absorption in the Phase II study.

Altus, whose technology enables it to develop enzyme replacements that can be delivered orally instead of by injection, is testing a product that replaces the enzymes lipase, amylase and protease. The capsule, taken at mealtimes, would replace enzyme-replacement drugs that must be taken 15 times or more each day.

Dr. Root, of USVP, pointed to several factors that make Altus a relatively safe bet. It is clear which enzymes are deficient and the market for the existing drugs is worth \$200 million in North America and \$600 million worldwide. The main risks investors are taking are regulatory and execution-oriented as opposed to technical, he said. •