

# Inhaled Insulin is Dead. Long Live Inhaled Insulin

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**Summary:** In early March, Eli Lilly became the third major pharmaceutical company to scupper its inhaled insulin program. Almost immediately the blogosphere began nailing inhaled insulin's coffin shut. *IN VIVO* thinks it's still too soon to deliver a eulogy. One company, MannKind, continues undaunted, despite the setbacks for its competitors, hoping to bring its inhaled insulin to market by 2010. Meantime, specialty pharmaceutical companies or glucose monitoring testing outfits might be interested in the inhaled programs spurned by Big Pharma, but only for the right price.

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## Inhaled Insulin is Dead. Long Live Inhaled Insulin

Ellen Foster Licking

On Friday, March 7 **Eli Lilly & Co.** confirmed rumors that had been swirling for much of the day: the company had terminated development of its Phase III inhaled insulin, *AIR* insulin, and returned all rights to partner **Alkermes Inc.**, due to higher regulatory and commercial hurdles. [W#200221047]

In the space of just five months, Lilly became the third major pharmaceutical company to abandon inhaled insulin. Last fall, **Pfizer Inc.** unceremoniously dumped *Exubera*, giving product rights back to partner **Nektar Therapeutics Inc.** and paying a \$135 million termination fee for the privilege [W#199520015]; in January, **Novo Nordisk AS** also announced it was scrapping its Phase III inhaled insulin program, which uses **Aradigm Corp.**'s **AERx** liquid aerosol system. [W#199820397] (See "Novo Scraps Inhaled Insulin," The IN VIVO Blog, *January 15, 2008*.) Lilly's news was particularly shocking, however, because the management team had repeatedly emphasized its commitment to the product in recent earnings calls and investor presentations.

Almost immediately, the blogosphere and mainstream press began nailing inhaled insulin's coffin shut. Since Pfizer launched *Exubera* in early 2007, it has become painfully obvious that most of the inhaled insulins in development or on the market are simply more convenient ways to deliver a drug that's already available in injectable form. This lack of differentiation—coupled with advancements in technologies that take the sting out of insulin shots and the rise of new drugs that significantly delay a patient's need to start insulin therapy—mean the commercial opportunities for these products are a far cry from the blockbuster sales once forecast. (See "*Exubera's Problem: It's Still Just Insulin*," IN VIVO, *May 2007* [A#2007800077].)

But even if that's the case, it's too soon to deliver inhaled insulin's eulogy—although the price tags of any future licensing deals will certainly reflect these products' straitened circumstances. One company that will be closely watched in the post Lilly/Alkermes fallout is **MannKind Corp.**, whose un-partnered *Technosphere Insulin (TI)*, is in Phase III trials and could launch as soon as 2010.

### For Lilly, *Byetta* Trumps Insulin

There's no doubt that Lilly's news announcement came as a huge shock to both Alkermes and its investors. For the past five months, the pharma has steadfastly championed the *AIR* insulin product. In the October earnings call, Lilly's president and COO John Lechleiter insisted: "We're not backing away an inch from either the program that we've got currently now in the middle of Phase III or our plans to go forward and file, I believe, in 2009." At January's JP Morgan conference and again on the company's February 7, 2008 earnings call, Lechleiter talked up the reasons why *AIR* insulin would succeed where Pfizer's *Exubera* had failed, citing a simpler, more convenient device, better dosing, and the availability of health economic data at the time of the product's launch.

To scupper the program just months before the conclusion of multiple late-stage clinical trials, including two-year safety studies in both type 1 and type 2 diabetes, seems, as one analyst noted, "a colossal waste." It's also incredible given the emphasis Lilly management had placed on an ongoing head-to-head study of *AIR* insulin versus **Sanofi-Aventis**'s long-acting once-daily injectable insulin glargine (*Lantus*). Had those still-blinded data indicated *AIR* insulin's superiority, Lilly would have been in the enviable position of demonstrating the medical benefits—in a real world setting—of inhaled insulin to patients, physicians, and payors. (See "*Insulin Delivery: Still Waiting to Exhale*," IN VIVO, *December 2007* [A#2007800186].)

Surely that would have provided the product with serious marketing advantages: Sanofi's *Lantus*, after all, is the starter insulin of choice for type 2 diabetics failing oral medications, and the company is marketing it aggressively. In February, the French company announced that 2007 sales of the drug grew by 29% to more than \$2.8 billion. And Kelly Close, founder editor-in-chief of *Diabetes Close Up*, a newsletter focused on the

business of diabetes, notes that total sales of long-acting insulins such as *Lantus* and Novo Nordisk's insulin detemir (*Levemir*), increased roughly 35% to \$3.3 billion over that same period.

As part of its March 7 announcement, Lilly emphasized that its decision was not motivated by safety concerns, but "rather was a result of increasing uncertainties in the regulatory environment, and a thorough evaluation of the evolving commercial and clinical potential of the product compared to existing medical therapies." Just weeks before, the US Food & Drug Administration issued new draft guidelines related to diabetes treatments. In particular, the agency recommended ratcheting up the requirements for products developed to treat type 2 diabetes, citing the growing number of people afflicted with the disease, as well the increasing complexity of treatment options. The agency now proposes that at the time of either a new drug application (NDA) or a biologics license application (BLA) that "Phase III trial data be available for at least 2,500 subjects exposed to the investigational product with at least 1,300 to 1,500 of these subjects exposed to the investigational product for 1 year or more, and at least 300 to 500 subjects exposed to the investigational product for 18 months or more."

It's not entirely clear whether Lilly had the patient numbers to meet these new requirements. When queried, Timothy Coulom, part of Lilly's public relations team, responded via e-mail: "There were approximately 2,400 type 2 patients enrolled in our Phase III trials. There were two-year safety trials for both type 1 (385 patients) and type 2 patients (414 patients)." With those patient numbers, it seems unlikely that the FDA would have created a stink upon submission of *AIR* insulin's NDA. After all, the drug is not a clone of rosiglitazone (*Avandia*), which recently received an additional black-box warning due to potential cardiovascular side effects. (See "*The Avandia Penumbra: Remapping Diabetes Drug Development*," The RPM Report, November 2007 [A#2007500190]; and "*Avandia's Black Box: FDA Office of New Drugs Wins*," The RPM Report, December 2007 [A#2007500207].) Still, the potential for ambiguity clearly had Lilly rattled: "There is uncertainty regarding how the FDA would view trials that initiated prior to the publication of this draft guideline," Coulom emphasized in his e-mail.

Industry watchers note that if Lilly had truly believed in the product's commercial prowess, it would have pushed for approval with the existing dataset and started additional safety studies as part of a postmarketing commitment. And Coulom admits that regulatory uncertainty "was not the sole driver for the decision." Clearly, the drastically curtailed commercial opportunities for the product played a role, especially given the other products in Lilly's diabetes portfolio, which include a partnership with **Amylin Pharmaceuticals Inc.** to co-develop and co-promote the incretin mimetic exenatide (*Byetta*), a twice daily injectable GLP-1 analog that has enjoyed rapid uptake since its mid-2005 launch, generating nearly \$177 million in sales in the last quarter of 2007 alone. [W#200220729]

But the real game-changer in Lilly's pipeline is its extended-release version of exenatide, a once-weekly injection of *Byetta* that the company developed with partners Amylin and, ironically, Alkermes, and that could be submitted to the FDA for approval in the first half of 2009. David Kliff, author of the *Diabetic Investor* newsletter, believes so-called *Byetta LAR* (long-acting release) will completely alter the way type 2 diabetics are treated. "It's the ultimate in convenience. There are no fingersticks and no need to count carbohydrates. It provides an average 2% drop in HbA1c levels, results in weight loss, and it's a once-a-week drug. That's a grand slam," he says. But as *Byetta LAR*'s value becomes more obvious, it's also true that competing GLP-1 analogs from Novo Nordisk and Sanofi are in development. In particular, many analysts expect Novo's liraglutide to steal market share from the *Byetta* franchise; data suggest the drug could be twice as effective as Amylin's and won't come with the worrisome side effect of neutralizing antibodies. In addition, it's administered with a smaller-gauge needle, meaning injections could be less painful for patients. (See "*Novo Nordisk: Riding High on Diabetes*," IN VIVO, June 2007 [A#2007800093].) Thus, with the potential for great profits from both *Byetta* and *Byetta LAR*, as well as looming competition from abroad, perhaps Lilly management was forced to make the hard decision to sacrifice the product with the smaller chance of commercial success—inhaled insulin—to focus on the more likely winners: its GLP-1 analogs.

Exhibit 1

## Inhaled Insulin: Partners Likely to Be Few and Fickle

Lilly's abrupt termination of its agreement with Alkermes is only the latest in a long string of inhaled insulin deals to go awry. Here's a look at the fates of various inhaled insulin developers.

COMPANY/PARTNER (DATE) (PRODUCT)	OUTCOME
Aerogen/Becton Dickinson (2000) (AeroDose)	Deal lasted one year. Aerogen, having stopped <i>Aerodose</i> development in 2003, was acquired by Nektar in 2005 for \$32 million.
Alkermes/Lilly (2001) (AIR insulin)	Agreement terminated March 2008. Alkermes retains rights to the IP surrounding AIR insulin and has the ability to purchase Lilly's clinical trials data for an as-yet-undetermined price.
Aradigm/Novo Nordisk (1998) (AERx iDMS)	Novo Nordisk terminated the agreement in January 2008 to refocus its inhaled insulin business on the delivery of long-acting insulin. Aradigm, meantime, plans to reinvent itself as a respiratory specialty pharma.
Dura/Lilly (1998) (Spiros)	Signed a partnership in 1998, only to have it dissolve shortly before Lilly inked its deal with Alkermes in 2001. In 2000, Elan acquired Dura for \$1.69 billion and tabled Phase I trials of <i>Spiros</i> .
Kos (Insulin breath-activated inhaler)	Abbott inherited Kos' inhaled insulin when it purchased the company in 2006. Abbott has remained mum on the inhaler's development—Phase II trials are supposedly ongoing. Recent events make it unlikely that Abbott will funnel additional resources into the program.
MannKind (Technosphere Insulin)	MannKind is the last competitor in the inhaled insulin space. Is looking for a partner but is prepared to go it alone, thanks to the deep pockets of founder and CEO, Al Mann. Success hinges on whether the company's apparently highly differentiated insulin acts as advertised.
Nektar/Pfizer (1995) (Exubera; next-generation inhaled insulin)	Pfizer jumped ship in October 2007, agreeing to pay Nektar a \$135 million break-up fee. Nektar continues to try to find a partner for either or both products. The company plans to table the program if no partner is found by June 2008.

SOURCE: Windhover's Strategic Transactions Database; company reports

### Partners Spurned

Where does this leave Alkermes? Four months ago, Alkermes' chairman Richard Pops told *IN VIVO*, "Inhaled insulin has been in and out of favor two or three times since we started working on it." But never have things been this bleak. "In addition to explaining their technology to potential partners, they also have to explain why there still is a market," says Ian Sanderson, an analyst with Cowen and Co. Ironically, Alkermes is now traversing the same path **Dura Pharmaceuticals Inc.** was forced to negotiate in 2001. Back in 1998, Lilly inked a deal with Dura to deliver inhaled insulin via the biotech's proprietary *Spiros* inhaler. [W#199820619] But Lilly ended the agreement to enter into an alliance with Alkermes that ultimately became the AIR insulin project. Dura, at least had the advantage of **Elan Corp. PLC**'s deep pockets—Elan had acquired the drug delivery play about a year prior for \$1.69 billion. [W#200010197]

Alkermes now has full rights to AIR insulin, but it's unlikely that ongoing Phase III trials will be completed. That's because those data are owned by Lilly. A termination clause in the agreement gives Alkermes the right

to purchase all regulatory submissions and related data, but as *IN VIVO* went to press, neither Alkermes nor Lilly had disclosed whether the companies had determined a pre-set price for this information. Moreover, it's not clear if Lilly has imposed a time limit on Alkermes' decision in the matter. That kind of ticking clock could make it difficult for Alkermes to find a suitable partner. And even without any time limit, uncertainty as to whether potential suitors would even have access to the Lilly Phase III data during the partnering negotiations makes it unlikely that interested parties would be willing to take on all the risks associated with *AIR* insulin.

It's possible that either specialty pharmaceutical companies like **Forest Laboratories**, **Cephalon Inc.**, or **KingPharmaceuticals Inc.**, which don't need to generate Big Pharma's outsized returns to make a profit on the product, might be interested in partnering with Alkermes. Alternatively, companies with glucose testing franchises, such as **Johnson & Johnson**, **Bayer AG**, and **DexCom Inc.** might also see this as opportunity to broaden their diabetes businesses. But presumably any licensor would force the Cambridge, MA-biotech to bear the lion's share of the remaining development costs.

To keep the program running at its current level, Cowen's Sanderson estimates Alkermes would need to sink \$40 million annually into *AIR* insulin's development. Alkermes has the cash to do this—thanks to a stake in **Reliant Pharmaceuticals Inc.**, Alkermes received nearly \$170 million in December following **GlaxoSmithKline PLC's** purchase of that start-up. [W#200710185] But that's a risky strategy: the same lung safety issues that dogged *Exubera* also plague *AIR* insulin. Moreover, there's no hard evidence that despite its convenience that the product actually works any better than today's injectable insulins. The company has already announced that it will use some of its Reliant windfall—up to \$93 million—to repurchase shares. Better, perhaps, for Alkermes to use the remaining cash to shore up the hole *AIR* insulin's demise leaves in its pipeline.

If there is any silver lining to the termination news, it's that Lilly forsook *AIR* insulin for *Byetta LAR*, a product in which Alkermes is also significantly invested. Alkermes' *Medisorb* technology was critical to creating the once-weekly injectable version of *Byetta* now being tested in the clinic, and the biotech stands to receive royalties estimated to be 7% of the product's sales.

Meanwhile, other inhaled insulin developers have struggled to find partners. Indeed, it's not even clear if Aradigm will pursue that option. Aradigm's *AERx iDMS* system was widely ridiculed as cumbersome, and clinical trials were delayed multiple times even before Novo Nordisk officially pulled the plug on the program. To protect itself, Aradigm had already begun to retrench, attempting to transform itself into a respiratory disease-focused specialty pharma developing liposomal drugs to treat inhalation anthrax and the lung infections associated with cystic fibrosis.

And despite months of trying, Nektar has had no takers for either its next-generation insulin, which is in Phase I trials, or *Exubera*, which is already approved. Meantime, on Nektar's February 2008 earnings call, CEO Howard Robin reiterated that discussions with potential partners "are continuing at a high level." But he also warned that absent a partnership by June 30 of this year, Nektar would stop investing in its inhaled insulin program and focus on other projects, such as its inhaled amikacin, a Phase II antibiotic that it being co-developed with Bayer. [W#200720545]

Even if there are potential partners for Nektar's insulins, Sanderson warns that Lilly's recent actions mean "deal terms just got cut." Still, unlike Alkermes, there's at least one advantage for Nektar. It can afford to partner its programs for a smaller dollar value because the bulk of the development costs have already been paid for. And since most analysts have completely discounted the company's inhaled insulin program in their forecasts, even a small deal would be viewed positively. "At this point, anything Nektar gets is a real bonus," says Sanderson.

## MannKind Stands Alone

Tepid interest for an inhaled insulin plus drastically reduced deal terms could spell trouble for MannKind, which has ever struggled to find a partner for *Technosphere Insulin*. To date, MannKind's CEO and controlling shareholder, Alfred Mann, has been bankrolling the company, investing more than \$560 million and promising loans of an additional \$350 million to fund the product's development. Hakan Edstrom, MannKind's president and COO, is confident the company will find a partner and doesn't believe the event will necessarily hinge on the publication of Phase III data, which are due out later this year. "Companies we are in discussions with understand that we have a different product," he claims.

Indeed, MannKind still has its supporters. Aileen Salares, an analyst with Leerink Swann, remains optimistic about MannKind's prospects, predicting \$1 billion in revenue by 2015. But unlike Edstrom, she acknowledges that the company may be forced to wait to partner its insulin until it finishes pivotal trials and files an NDA with regulators. But she is convinced that the company has an opportunity to capture significant market share, in particular because *TI*'s pharmacokinetic properties are so vastly different from other insulins—injectable or inhaled—on the market or under development. "The discontinuation of other products doesn't change our view of MannKind's," says Salares.

But Salares seems to be in the minority. The company felt the need to issue a press release Monday, March 10 after investors fled the stock, reaffirming its commitment to *TI*'s continued development and spelling out the differences between its rapidly acting inhaled version and those of Lilly, Pfizer, and Novo Nordisk. "None of those products offer any advantages over injectable rapid acting insulin analogs," the company stated in its release. In contrast, according to the company, *Technosphere Insulin* has shown important benefits in the following areas: a significant reduction in post-meal-time glucose excursions, approaching the levels seen in normal people; a lower risk of hypoglycemia; no weight gain, and potentially weight loss; and a dosing regimen that significantly simplifies a patient's treatment. "Put all those together, and it's a compelling offering," Edstrom later told *IN VIVO*.

Undoubtedly—if *TI* works as advertised. "It sounds too good to be true," notes Close of Close Concerns. But unlike Lilly and its partner Alkermes, MannKind won't have to worry that its trials aren't robust enough to satisfy the FDA. "We understand that physicians and regulatory agencies are cautious about a new route of administration," says Edstrom. In structuring our trials, "We treated *TI* as if it were a new chemical entity," testing the product in more than 5,000 diabetics, he says. Among the studies performed by MannKind: a two-year pulmonary safety trial of 2,050 patients recently recognized by the American Association of Respiratory Care as setting new quality standards in the conduct of clinical trials.

*TI* illustrates one of the great ironies of drug delivery. The ultimate success of a product depends as much on its uniqueness as it does on the device used to deliver it. (See "*The Drug Delivery Road Gets Tougher*," *START-UP*, December 2007 [A#2007900223].) That MannKind's *MedTone* inhaler is small and patient-friendly is undeniably important. But ultimately, if *TI* prevails in the marketplace, it will do so not because of its highly engineered inhaler but because its insulin outperforms existing versions. That point ought to worry specialty pharma building businesses around drug reformulations and re-profiling. It suggests that there's a new standard in drug delivery—to drive market adoption, it's imperative that a company treat its drug like an NCE. And that's a change certain to roil the economics associated with the sector.