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Breath Of Fresh Air For Cystic Fibrosis Drug Pipeline

The outlook for cystic fibrosis drug development now is “a very different story than even five years ago,” according to Cystic Fibrosis Foundation President Robert Beall.

“We’re really starting to see the return now on the investments,” Beall told *Pharmaceutical Approvals Monthly*. “We’ve never had a pipeline like this ... we’re leveraging our investment.”

The Cystic Fibrosis Foundation, which invests more than any other disease foundation in the U.S., is a model for venture philanthropy in orphan diseases.

CFF’s nationwide network of care centers and patient registry follows approximately 23,000 diagnosed CF patients – about 80-90 percent of all diagnosed CF patients in the U.S., says CFF President Robert Beall.

The foundation’s therapeutics arm has invested over \$300 million in early stage development to entice firms to look at CF drugs.

Today, more than 15 therapies specifically indicated for CF patients are in development or in clinical trials; another 15 previously used for other indications are also testing in CF patients (*see chart*).

A marker of the maturing pipeline was reached on Nov. 16, when Gilead submitted an NDA for aztreonam lysine, a monobactam antibiotic for inhalation developed for CF patients with pulmonary *Pseudomonas aeruginosa* (Pa) infection.

Only two drugs specifically developed for cystic fibrosis patients have been approved since the disease was characterized in 1938, both in the last 15 years.

“Chronic pseudomonal airway infection represents the single greatest cause of morbidity and mortality for people with cystic fibrosis, and with a limited number of inhaled antibiotics, there remains a significant unmet medical need,” A. Bruce Montgomery, senior VP and head of respiratory therapeutics at Gilead, said.

The Gilead filing comes one decade after approval of the first and to date only inhaled antibiotic specifically formulated for Pa infections in CF patients: FDA approved Novartis’ inhaled tobramycin formulation **TOBI** in December 1997.

The first drug approved specifically for CF was Genentech’s mucolytic **Pulmozyme** (dornase alfa) in December 1993.

CF Foundation Primes the Pump

In 2000 two milestones occurred: CFF established a therapeutics division to facilitate drug discovery and development, and scientists mapped the Pa genome.

Beall believes the non-profit therapeutics division, CF Foundation Therapeutics, ushered in a “paradigm shift” – early stage money, new technology, newborn screening, access to a hands-on care network, and new potential in prevention – to attract firms to the orphan disease.

By 2004 CFF was supporting two dozen potential therapies in their pipeline, including some of the first to address the CF gene’s genetic defects, first discovered in 1989 (*Pharmaceutical Approvals Monthly*, May 2004, p. 6).

About 10 percent of the 23,000 patients in the foundation’s registry are in some form of clinical trial, Beall says, but “we have to double and triple that in the next few years.”

Another challenge is “always how receptive FDA is going to be,” Beall said. “How can we get drugs safely, effectively, and efficiently to patients? What are the outcomes [FDA is] willing to accept?”

In CF, as in all drug development, a proportion of projects fail. In the last two years, two relatively high-profile projects were terminated. Boehringer Ingelheim’s anti-inflammatory leukotriene B4 antagonist amelubant (BIIL-284) was found to significantly increase risk of pulmonary adverse events; Phase II stopped early in July 2004. Amelubant also failed in a rheumatoid arthritis trial (*Pharmaceutical Approvals Monthly*, November 2004, p. 12).

In March 2005, Targeted Genetics’ aerosol gene therapeutic tgAAVCF did not meet its primary endpoint in Phase II, which was stopped early.

The gene therapy setback was a disappointment because CF has long been considered a prime candidate for gene therapy: the disease is caused by a defect in a single gene, which produces the CF transmembrane conductance regulator protein.

CFFT has continued to support gene therapy. On Dec. 11, it announced a milestone payment to Copernicus for development of a non-viral CFTR gene replacement product. Copernicus’ approach, being tested in early human studies, uses compacted DNA nanoparticles delivered to the lung.

“We are fighting this disease from every angle,” Beall said. “We’re constantly taking advantage of technology – gene therapy, CFTR modulation, ion transport – all of these are shots on goal ... we haven’t put all of our eggs in one basket.”

Targeting Antibiotics To The Lung

Inhaled antibiotics for Pa have proven a fertile area of study. Following aztreonam lysine, another candidate is in Phase III: Novartis/Nektar’s next-generation tobramycin product *TIP* (tobramycin inhaled powder). TIP may allow patients to receive higher doses than those given systemically, the company says.

Developers of inhaled antibiotics have the advantage of experience with approved injectable formulations. In CF patients, inhaled drugs are preferred for patient compliance and reduced toxicity.

Aztreonam is sold by Elan in an injectable, *Azactam*, that formulates aztreonam with arginine. Gilead’s product, in contrast, is aztreonam lysine. Azactam, approved by FDA in 1986 and originally marketed by Bristol-Myers Squibb, is considered a potent antibiotic against Gram-negative aerobic pathogens.

Gilead acquired aztreonam lysine through a 2006 investment in Corus Pharma, as part of its efforts to build a respiratory franchise. Two other Gilead candidates are in early stage development for CF.

The pivotal trial package supporting the aztreonam lysine NDA comprised a Phase III study (AIR-CF1) that compared the drug with placebo, and a Phase III (AIR-CF2) that tested a 28-day course of aztreonam lysine followed by a 28-day course of TOBI.

The AIR-CF1 trial was the first Phase III trial in CF to use a patient-reported outcome tool – the CF Questionnaire-Revise – as its primary endpoint. AIR-CF1 showed “improvement in respiratory symptoms” in CF patients with pulmonary Pa, Gilead reported.

AIR-CF2 demonstrated that inhaled aztreonam lysine "significantly delayed the time to need for inhaled or [I.V.] antibiotics following a course of inhaled tobramycin," Gilead continued. Both studies found "improvements from baseline in respiratory function."

"Gilead believes the data support first-line use for aztreonam lysine," the company told *Pharmaceutical Approvals Monthly*. "We believe alternating monthly cycles with TOBI are more likely in patients with more severe disease."

Transave is trying to improve pulmonary delivery of antibiotics by formulating the drug with liposomes. *Arikace* (liposomal amikacin for inhalation) is in Phase II for CF patients with Pa. Arikace is formulated with Transave's Sustained Release Lipid Inhaled Targeting Technology; the company hopes to deliver high concentrations of amikacin locally in the lung with less frequent dosing.

Nektar, which is working with Novartis on TIP, has partnered with Bayer on *CIP* (ciprofloxacin inhaled powder). CIP, which is in Phase I, draws on Bayer's experience with ciprofloxacin, which the company introduced in 1987 as *Cipro*.

Gilead's second candidate, GS-9310/11, is an inhaled product combining tobramycin and fosfomycin, the active ingredient in Zambon/Forest's *Monurol*. Gilead is currently enrolling patients in two Phase Ib trials.

Mpex says its inhaled levofloxacin solution MP-376 will kill pathogens resistant to tobramycin and aztreonam. Mpex plans to initiate Phase II in 2008.

Kalobios is developing an anti-infective treatment for CF based on an antibody rather than a small molecule antibiotic. KB001 is in Phase I.

Chloride Ion Channels

Fewer products directed at CF patients' deficient salt transport are in the clinic than inhaled anti-infectives, but one is in Phase III. The deficient CFTR protein prevents the transport of chloride ions between cells, leading to CF's characteristic thick sticky mucus.

CFF head Beall hopes Inspire's denufosal tetrasodium will be approved in 2-3 years. The P2Y2 agonist has multiple pharmacologic actions, according to Inspire, including hydration of the airways by stimulating chloride and liquid secretions on the epithelial cell surface and inhibition of epithelial sodium absorption.

Inspire completed enrollment of its Phase III TIGER-1 trial of inhaled denufosal (INS-37217) in October. Top-line efficacy data is expected in mid-2008. Inspire also expects a final study report from a 2-year inhaled carcinogenicity study in the second half of 2009.

TIGER-2, the second pivotal trial, will begin in North America in early 2008 and expand enrollment internationally in the second half of the year.

Denufosal is envisioned as an early intervention treatment for patients with mild CF lung disease.

Lantibio says that its product Moli1901, a stable 19-residue polycyclic peptide, appears to increase chloride transport and fluid secretion. Lantibio holds a U.S. IND for the product, but it is in active development in Europe with AOP Orphan. An aerosolized formulation of Moli1901 has reached Phase II in Europe.

Sucampo's cobiprostone (SPI-8811) is in development for multiple GI conditions. The company is also pursuing use in CF due to the product's activation of the chloride ion channel CIC-2, a different chloride ion

transport process than that which is defective in CF patients that could potentially act as an alternate chloride channel.

Sucampo conducted a Phase II study of oral cobiprostone in CF patients in 2003. The trial produced inconclusive results for chloride secretion, convincing the company to focus initial R&D on treatment of GI disorders associated with CF. A Phase II dose-ranging trial is planned for the first half of 2008 for CF-associated GI disorders, with development of an inhaled formulation of SPI-8811 planned in the future.

Gilead recently licensed an epithelial sodium channel inhibitor that may increase hydration of the epithelial surface. Gilead licensed the preclinical ENaC inhibitor P-680 from Parion Sciences in August. P-680 could be "synergistic" with aztreonam lysine, Parion suggested: P-680 would hydrate mucosal secretions and allow the antibiotic to penetrate better.

Debiopharm/Dyax's depelestat is currently in Phase IIb to define dosing for Phase III trials. After completing Phase II, the company says, it will look for marketing partners with CF and pulmonary experience.

Debiopharm describes depelestat as "a new anti-inflammatory drug targeted against neutrophil mediated inflammation, designed to prevent pulmonary CF lesions." Depelestat, an engineered protein inhibitor of human neutrophil elastase, has been tested in Phase IIa; Debiopharm is planning a Phase IIb trial in CF patients aged 6 years and older.

Beyond Novel Pharmaceuticals

Other clinical trials, many sponsored by CFF, are looking at issues related to antibiotic resistance and susceptibility, using approved products like azithromycin and hypertonic saline for CF, comparing effectiveness of tobramycin and ciprofloxacin in children with CF and expanding indications to infants.

Newborn screening tests for CF – offered or required in all but eight U.S. states – will increase awareness of the disease, and, along with new and improved therapies, will help manage the disease but "will not provide a cure," Jackie Zirbes, CF lung transplant coordinator at the University of Minnesota's Cystic Fibrosis Center, said. Guidelines for treatment of newborns to accompany screening should be published soon.

Currently about 80 percent of patients are diagnosed by age 4, Beall said, but "we want to see that if we can identify these patients very early, can we postpone the development of symptoms with early intervention?"

"We have every possible chance to restore this patient to normalcy," Beall added. "If we can intervene [at birth] and reverse that [lung] deterioration, we're adding decades to their lives."

Hypertonic saline, now being tested in infants in the U.S. after showing positive results in Australia, could push symptoms back by decades, Beall believes. By using hypertonic saline to prevent the mucus from thickening in infants' lungs, "maybe the infections and inflammatory responses won't start, and then you won't get lung destruction."

A cure that would correct the basic defect in the CFTR gene remains possible, Beall said, but he also noted a goal of reversing of lung deterioration. "Somebody at 20 or 40 percent lung function might not go back to 100 percent, but we can reverse that decline."

– *Becky Jungbauer and Bridget Silverman*

Cystic Fibrosis Pipeline			
Product	Sponsor	Indication	Phase
Anti-infectives			
TOBI (tobramycin)	Novartis	Inhaled antibiotic for Pa in CF	Approved 12/22/1997
Aztreonam lysine	Gilead Sciences	Inhaled antibiotic for pulmonary Pa in CF	Filed NDA 11/16/2007
TIP (tobramycin inhaled powder)	Novartis/Nektar	Inhaled dry powder antibiotic for Pa in CF	Phase III
Arikace (liposomal amikacin for inhalation)	Transave Pharmaceuticals	Liposomal formulation of antibiotic amikacin for Pa in CF	Phase II
KB001	Kalobios	Anti-infective antibody for Pa in CF	Phase I
MP-376	Mpex Pharmaceuticals	Levofloxacin solution for inhalation for Pa in CF	Phase I
GS-9310/11 (fosfomycin, tobramycin)	Gilead Sciences	Inhaled combination antibiotic for pathogens underlying Bronchiectasis and CF	Phase I
CIP (ciprofloxacin inhaled powder)	Bayer/Nektar	Inhaled dry powder antibiotic for infections associated with CF	Phase I
Pa: Pseudomonas aeruginosa CF: cystic fibrosis			
CFTR gene and protein modifiers			
VX-770	Vertex Pharmaceuticals	Impacts CFTR protein function	Phase II
tgAAVCF	Targeted Genetics	Adeno-associated viral vector delivery of CFTR gene	Terminated Phase II 3/2005
PTC124	PTC Therapeutics	Targets nonsense mutation in CFTR gene	Phase II
Compacted DNA	Copernicus	Non-viral nanoparticle formulation of CFTR gene	Phase I
CFTR: CF transmembrane conductance regulator			
Salt transport			
Denufosal tetrasodium	Inspire	Inhaled P2Y2 receptor agonist	Phase III
Cobiprostone (SPI-881)	Sucampo	Ion transport modulator	In development
Moli1901	Lantibio	Inhaled ion transport modulator	Phase II (Europe)
P2Y2: Purinergic receptor P2Y, subtype 2			
Anti-inflammatory			
Depelestat (Debio 9701, Dyax DK-890, EPI-hNE4)	Debiopharm/Dyax	Inhaled neutrophil elastase inhibitor	Phase II
Amelubant (BIIL-284)	Boehringer Ingelheim	Anti-inflammatory leukotriene B4 antagonist	Terminated Phase II 7/2004
Inhaled glutathione	Cystic Fibrosis Foundation (CFF)	Inhaled antioxidant	Phase II
HE2000	Hollis-Eden/CFF	Immune-regulating hormone	In development
Mucolytics			
Pulmozyme (dornase alfa)	Genentech	Inhaled solution to manage CF and improve lung function (in conjunction with other therapies)	Approved 12/30/1993
Hypertonic saline	CFF	Inhaled solution to improve lung function	Trials ongoing

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