# Trends-in-Medicine

**May 2008**

*by Lynne Peterson*

## SUMMARY


♦ **IPF:** Data from a Japanese trial showed InterMune/Shionogi's pirfenidone effective in preserving vital capacity, but the trial had a high dropout rate, and the side effects – especially photosensitivity – could be problematic. The U.S. pivotal trial has a slightly different endpoint – FVC instead of VC – but the FDA also wants to see a mortality trend or benefit.

♦ **PAH:** United Therapeutics' inhaled Viveta met the primary endpoint in its pivotal trial, but doctors weren't sure that the improvement in 6-minute walk was as robust as they would like to see clinically, though Viveta is easier to administer than Actelion's Ventavis. ♦ PK data on United Therapeutics' ***oral*** Remodulin suggest it may turn out to be both effective and safe, though some patients may need TID rather than BID dosing, and patients may need individualized titration. ♦ Drugs approved for other indications that appear promising in PAH: Bayer's Nexavar and Novartis's Gleevec.

♦ **COPD:** Forest/Almirall's aclidinium appears comparable in efficacy and safety to Pfizer's Spiriva, but it failed to differentiate itself except in terms of the delivery device, which is very slick – but Spiriva will soon have an interesting new device as well. ♦ Pneumonia is a risk with inhaled corticosteroids, but that is not a barrier to new combination products, and the risk is unlikely to require longer or larger trials.





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## AMERICAN THORACIC SOCIETY (ATS)

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There were new data on several drugs in development for idiopathic pulmonary fibrosis (IPF), pulmonary arterial hypertension (PAH), and chronic obstructive pulmonary disease (COPD) at ATS this year. However, pulmonologists, cardiologists, and other doctors questioned said there was little that would immediately and significantly change what they would do when they go home.

## IDIOPATHIC PULMONARY FIBROSIS (IPF)

IPF is a specific form of chronic, incurable, fibrosing disease that makes breathing very difficult. It has no known cause. About 50,000 Americans have IPF, which has a prevalence of 13-20 per 100,000 people in the U.S. Median survival was thought to be 2-3 years, but as more patients get diagnosed earlier, an expert said this may have changed to 4-5 years.

Ideas about the course of this disease are changing. The conventional wisdom was that patients start with a normal lung, and over time, in a linear fashion, the normal lung tissue is replaced with fibrosis. Dr. Harold Collard, a pulmonologist from the University of California, San Francisco (UCSF), said, "We thought lung function declines in a steady rate over time…starting with an asymptomatic patient with normal lung function, development of cough and shortness of breath, followed by severe limitations, and then death…Observations from clinical trials have shown that the decline in lung function is quite different from what we thought…(What we've learned is that) there is a relatively stable course, punctuated by acute episodes of worsening, which can be fatal or cause significant morbidity – a step-like decline in lung function. Acute exacerbations are an important clinical cornerstone of that progression."

Another UCSF expert, Dr. Talmadge King, said there are three courses the disease can take:

1. **Chronic, slow progressive impairment.** It was estimated that FVC (forced vital capacity) declines ~20 ml per year, which is higher than originally thought.
2. **Chronic slow progression with acute (<4 week) deterioration (periodic acute exacerbations).** This is the most common form. Patients seem to be going along well, then have a decline in lung function, but if they recover, they don't return to their prior level. Acute exacerbations are now thought to be a major cause of poor outcomes in IPF patients.
3. **Rapid onset and progression.** This is a small subset of IPF. These patients – who tend to be males and smokers – have symptoms <6 months before diagnosis, and the survival curve in this population is very poor.

Key issues in the management of IPF that need to be addressed to improve survival:

- **Acute exacerbations.** The current definition of an acute exacerbation is: an acute, clinically significant deterioration of unidentifiable cause in a patient with underlying IPF, but there is a debate going on over the correctness of this definition. Dr. Collard questioned whether this is an accurate definition. He said the annual incidence of mortality from acute exacerbations may be 10%-30%. Diagnostic criteria for acute exacerbations are:
  - Previous or concurrent diagnosis of IPF.
  - Unexplained worsening or development of dyspnea (≤30 days).
  - HRCT: bilateral "ground glass" and/or consolidation superimposed on a "UIP pattern."
  - No evidence of infection by endotracheal aspirate or BAL (bronchoalveolar lavage).
  - Exclusion of other causes (e.g., congestive heart failure or pulmonary embolism).
- **Pulmonary hypertension.**
- **Gastrointestinal reflux** (GERD) and chronic "silent" microaspiration. Some experts believe that GERD plays a role in IPF, suggesting that treating GERD can help prevent progression and/or acute exacerbations. One speaker claimed that 87% of IPF patients have GERD and that it ***possibly*** is linked to pathogenesis, though there is no hard evidence of that. He said, "You could argue that GERD treatment should be initiated. You should treat the symptoms at the very least. A symptom-based approach is probably reasonable."

Currently, there are no good therapies for IPF, but doctors commonly use a corticosteroid, azathioprine (AZA), and N-acetylcysteine (NAC), often in combination, and occasionally cyclosporine or an anticoagulant (warfarin). Dr. Collard said, "Most people treat with corticosteroids, but there are no data on their efficacy in this condition…To me, the data (on cyclosporine) are really unconvincing, but there are people who believe it is. The jury is still out…One study found a reduction (in progression) with Coumadin (warfarin)." Dr. King said, "Therapy should be discouraged until a firm diagnosis has been established. No data exist that adequately documents that any of the current treatment approaches for IPF improves survival or quality of life for patients."

The treatment for IPF also depends on the stage at diagnosis:

- **Mild-to-moderate** (FVC >50%). Treatment guidelines issued in 2000 suggested prednisone + AZA, but Dr. Ganesh Raghu, director of the Interstitial Lung Disease/ Sarcoid/Pulmonary Fibrosis Program at the University of Washington, said that was not based on any scientific evidence.
- **Severe** (FVC ≤50%). Lung transplantation may be an option, but survival is still limited, and lung transplantation has its own problems.

Dr. King said the current treatment paradigms are:

- **To relieve symptoms, improve exercise toleration, or improve health status** – Pulmonary rehabilitation and oxygen.
- **To treat complications and exacerbations** – New approaches are needed.
- **To prevent disease and reduce mortality** – Enroll patients in a randomized clinical trial of an experimental therapy. The only thing that has been shown to improve mortality is a lung transplant.

*What would Dr. King give a patient requiring drug therapy today?* He said, "Combined therapy with a corticosteroid, azathioprine, and NAC is probably the recommended treatment for those patients who want to be given therapy, who have been given adequate information on the merits and pitfalls of treatment, and who possess features consistent with a more likely favorable outcome – FVC >50% and diffusing capacity >40%. Less than that and they almost uniformly do not respond…Right now, this is probably what most of the experts would do…Current traditional therapy with steroids and azathioprine doesn't work…The IFGENIA trial showed that the combination (of a steroid, AZA, and NAC) appears to slow progression (decline in vital capacity or decline in diffusing capacity)…The study shows not much difference, but right now that appears to be the therapy of choice…There is no evidence it works…but if you want to try something, the best evidence is (triple therapy) slows progression, but the evidence is very poor."

However, there are two trials underway, both sponsored by the National Institutes of Health/National Heart, Lung, Blood Institute (NIH/NHLBI) and conducted by the major medical centers in IPFnet, that are expected to determine the value of currently used therapies:

1. **PANTHER-IPF.** This is a three-arm trial comparing NAC vs. placebo vs. NAC + AZA + prednisone in 390 treatment-naïve patients with mild-to-moderate IPF. There will be 130 patients in each arm, and the placebo arm is a "true" placebo arm. What will it mean if this trial is negative? Dr. Raghu said, "If all three arms decline the same way, that will tell us NAC is ineffective, that prednisone + AZA is finally buried for good, and no one should use it again for mild-to-moderate disease…One option (then) would be no treatment. Even now, you should consider a no-treatment option. You should be upfront with patients and say a no-treatment option should be considered."
2. **STEP-IPF.** This is a 170-patient trial of sildenafil in IPF patients with advanced disease. So far, 62 patients have been enrolled.

## IPF Therapies on the Horizon

### Actelion's Tracleer (bosentan)

In one trial, Tracleer, which is FDA-approved for pulmonary arterial hypertension (PAH) but not IPF, did not meet the primary endpoint, an improvement in 6-minute walk distance (6MWD). However, in a post hoc analysis, patients with biopsy-proven IPF had a delayed time-to-disease-progression or death with Tracleer, leading the company to undertake the ongoing BUILD-3 trial in patients with biopsy-proven disease. An interim report on that trial is expected later this year, and the full results are likely to be published in the fall of 2009.

### InterMune's pirfenidone

During ATS, the FDA granted fast-track status to pirfenidone, which generally means a faster regulatory review because it allows for rolling submissions. Pirfenidone was developed by a Japanese company, Shionogi & Co., and InterMune licensed non-Japan rights in 2002.

A double-blind, placebo-controlled, Phase II trial by Shionogi showed promising results in a subgroup of patients. That trial was stopped early by the DSMB because pirfenidone appeared to reduced acute exacerbations, which occurred in the placebo arm but not in the drug arm. Although pirfenidone failed to show a statistically significant benefit on the primary endpoint – the change in the lowest oxygen saturation ($SpO_2$) during 6-minute steady state exercise test (6MET) – it did show a benefit in the subset of patients who maintained $SpO_2$ >80% during 6MET at baseline, with the vital capacity decline significantly less for pirfenidone-treated patients.

Based on this subgroup, Shionogi undertook a one-year, double-blind, Phase III trial. Those results were presented at ATS, and the high dose met the primary and both secondary endpoints. The primary endpoint used in this trial was vital capacity (VC), which is different from the forced vital capacity (FVC) measure commonly used in U.S. IPF trials. The trial studied two different doses of pirfenidone (1800 mg and 1200 mg) in 267 patients (2:1 randomization). Patients in the high-dose arm started at 600 mg, and were titrated up to 1200 mg after 2 weeks, and then to 1800 mg after another 2 weeks. VC was measured every 4 weeks; $SpO_2$ was measured every 12 weeks.

Despite a high dropout rate, an intent-to-treat analysis, using last observation carried forward (LOCF), found the drug was effective in slowing the deterioration of vital capacity and improved progression-free survival (which was similarly improved with both doses). Dr. Takashi Ogura of the Kanagawa Cardiovascular and Respiratory Center in Yokohama, Japan, who presented the results, said it can't be determined whether the low dose is as effective as the high dose due to the small sample size. Yet, pirfenidone showed none of the benefits on reduction in acute exacerbations that was seen in the Phase II trial.

And the side effects – especially photosensitivity, anorexia, dizziness, and elevated gamma-GTP (a marker of liver enzymes) – were significant. Dr. Ogura said there was no elevation in ALT or AST, despite the elevated γ-GTP.

The photosensitivity occurred despite the use of sunscreens, but Dr. Ogura said 64% of cases were mild, 36% moderate, and none severe. Photosensitivity caused 11% of patients to discontinue the trial, 5% had the drug withdrawn, and 23% had a dose reduction.

*Asked why $SpO_2$ was chosen as a secondary endpoint*, Dr. Ogura said that Japanese regulators recommended it.

**1-Year Results of Phase III Japanese Trial of Pirfenidone**

| Measurement | Pirfenidone 1800 mg n=108 | Pirfenidone 1200 mg n=55 | Placebo n=104 |
|---|---|---|---|
| Completed the study | 63.0% | 72.7% | 70.2% |
| Smoking history | 4.6% | 18.2% | 12.5% |
| **Discontinuations** | | | |
| All discontinuations | 40 patients | 15 patients | 31 patients |
| Due to adverse events | 15 patients | 9 patients | 7 patients |
| Due to disease progression | 8 patients | 0 | 15 patients |
| Due to acute exacerbations | 4 patients | 2 patients | 4 patients |
| Due to other reasons | 3 patients | 4 patients | 5 patients |
| **Efficacy results** | | | |
| ***Primary endpoint:*** Vital capacity (VC) change from baseline *** | - 90 mL (p=0.0416 vs. placebo, Nss vs. 1200 mg) | - 80 mL (p=0.0394 vs. placebo) | - 160 mL |
| ***Secondary endpoint #1:*** Progression-free survival ** | (p=0.0280) | (Nss, p=0.0655) | --- |
| ***Secondary endpoint #2:*** Lowest $SpO_2$ during 6MET | - 1.70% | - 0.84% | - 1.53% |
| Acute exacerbations | 5.6% (Nss) | 5.5% (Nss) | 4.8% |
| **Adverse events** | | | |
| Death | 3 patients | 4 patients | 4 patients |
| Photosensitivity | 51.4% * | 52.7% * | 22.4% |
| γ-GTP elevated | 22.9% * | 21.8% | 9.3% |
| Anorexia | 16.5% * | 10.9% | 2.8% |
| Dizziness | 7.3% * | 0 | 0.9% |
| Abdominal discomfort | 2.8% | 7.3% * | 0 |
| White blood cell decrease | 3.7% | 5.5% * | 0 |
| Eczema | 0 | 5.5% * | 0 |
| Upper respiratory tract infection | 0.9% | 5.5% | 8.4% |
| Nasopharyngitis | 49.5% | 54.5% | 65.4% |

* p<0.05 vs. placebo.

** Defined as >10% decline in VC, acute exacerbation, or death.

*** Note that the primary endpoint was VC and not FVC.

InterMune is conducting two 72-week U.S. Phase III trials in the CAPACITY program:

- A 400-patient trial of high dose (2400 mg) pirfenidone vs. placebo.
- A 320-patient trial of high dose (2400 mg) pirfenidone vs. low dose (1800 mg) pirfenidone vs. placebo.

The U.S. doses are higher than used in the Japanese Phase III trial because of the body weight differences between Japanese (average 60 kg) and American patients, an InterMune official explained. CAPACITY completed enrollment in March 2007, with published results expected in 2009. The primary endpoint in both is FVC, and experts all agreed that this is a very good and approvable endpoint for an IPF trial.

*Do the results of the Japanese trial raise confidence that InterMune's CAPACITY trial will be positive?* Probably, but the question may be side effects, not efficacy. A speaker said, "The conduct of the trial has gone extremely well." However, another pulmonologist said two of her patients withdrew from the trial due to adverse events. Another expert said, "The key is the peer review process. Once the data are published in a peer-reviewed journal, I'll believe it…FVC is a good endpoint. Even a small difference in FVC in a *population* is clinically significant because some patients will have a real benefit…6MWD is not needed; FVC is a surrogate for survival."

**Other agents in development to treat IPF include:**

- **NOVARTIS's Gleevec (imatinib).**
- **FG-3109.** (*company unknown*)
- **GENZYME's GC-1008, an anti-TNF-β monoclonal antibody.** An open-label, single-dose, dose-escalation, Phase I PK study in 25 IPF patients presented at ATS showed that doses from 0.3 mg/kg to 8 mg/kg were well tolerated out to 140 days post-infusion. There were no dose-limiting toxicities, and the most common adverse events were fatigue and headache. There was one serious adverse event, a transient ischemic attack (TIA) at Day 38.

## PULMONARY ARTERIAL HYPERTENSION (PAH)

The number of PAH patients is continuing to increase, doctors said. They ascribed this to two factors: increasing awareness (and thus diagnosis and treatment) and an increase in the incidence (due to new causes). At least for the next year or so, doctors expect patient numbers to continue to grow.

There are three currently approved classes of drugs to treat PAH.

1. **Prostacyclin analogs:**
   - GlaxoSmithKline/Myogen's Flolan (epoprostenol).
   - United Therapeutics' Remodulin (treprostinil).
   - Actelion's Ventavis (iloprost).
2. **Endothelial antagonists:**
   - Gilead's Letairis (ambrisentan), approved in 2007.
   - Actelion's Tracleer (bosentan), approved in 2001.
   - Encysive's Thelin (sitaxsentan). Approved in Europe and Canada but not the U.S.
3. **Phosphodiesterase-5 inhibitor:** Pfizer's Revatio (sildenafil).

Combining these therapies is also an option. But Dr. Hossein Ghofrani, head of the Pulmonary Hypertension Division at the Giessen University in Germany, commented, "Currently, we are in a stage where we can reduce symptoms but not reverse the disease. I think we are still far away from that…We haven't healed any patients so far with any of these treatments." At a symposium sponsored by Encysive, Dr. Stuart Rich, a cardiologist from the University of Chicago who specializes in pulmonary heart disease, argued that none of these agents really works, and he suggested that high dose calcium channel blockers may be more effective. However, he admitted that most of the ~1,400 PAH patients in his center's database are or were on one or more of the approved PAH drugs, most often an IV prostacyclin.

Dr. Rich challenged the audience to show him proof they work. He said, "Patients are surviving better (since these drugs were introduced)…(but) I have yet to see any evidence these drugs work on the pulmonary circulation in humans…nor have I seen evidence that the survival of patients on modern therapy is due to anything more than warfarin, which appears to be able to account for all the survival (improvement)…Yes, patients are living longer, being cared for better, walking a little farther…(But) is the treatment effective? I would have to say in all candor...that I don't know that any of these drugs truly (work)…If you believe these drugs reverse disease, work more than 12 weeks, and that patients don't decline at one year, show me."

Researchers are trying to find a biomarker to use in the treatment of PAH. Dr. James White of the University of Rochester presented data suggesting that serum angiopoietin-2 levels might be a valid biomarker in PAH. His data came from a substudy of the randomized, multicenter, double-blind, 12-week TRUST-1 trial. TRUST-1 was conducted entirely in treatment-naïve patients in India and compared United Therapeutics' IV Remodulin (treprostinil) to placebo. At the time the study was done, there were no approved PAH therapies in India, and there still aren't any, plus all patients were offered free life-time drug therapy (including the delivery system), so he said the trial was ethical.

The treprostinil biomarker substudy planned to enroll 125 patients but only enrolled 44 (and only 16 of these provided both baseline and Week 12 serum samples). The substudy analyzed a variety of possible biomarkers: angiopoietin-1 and 2, MMP-2 and -9, VEGF, PDGF-AB, FGF, IL-1β, IL-6, IL-8, and IL-13. Only angiopoietin-2 appeared to correlate with disease progression or treatment, and angiopoietin-2 changes

were associated with increases in the 6MWD (p=0.0032), accounting for ~25% of the improvement in that measure. Dr. White concluded, "A study like this lets us say angiopoietin-2 is potentially interesting."

**TRUST-1 Biomarker Results**

| Measurement | IV Remodulin n=30 | Placebo n=14 | p-value |
|---|---|---|---|
| ***Primary endpoint:*** 6MWD change from baseline | + 67 meters | - 26 meters | 0.033 |
| **Biomarker findings with Remodulin** | | | |
| Angiopoietin-2 | Elevated above normal range at baseline, declining to normal range at Week 12 | | |
| VEGF | Elevated at baseline and stayed high or increased during treatment | | |
| PDGF | Elevated at baseline and stayed above normal | | |
| bFGF | Normal at baseline and increased over the course of the study | | |
| MMP-9 | Elevated at baseline and remained elevated at Week 12 | | |
| MMP-2, Angiopoietin-1, IL-1β, IL-6, and IL-13 | Normal at baseline and didn't change over the treatment period | | |

6MWD is a commonly used primary endpoint in PAH trials. Dr. Janet Pope, a rheumatologist from Canada, said, "I do think 6MW actually is seemingly reproducible in these trials …It always functions better than placebo. And that is how things get approved. It does seem to translate into a significant subset of patients improving over the long term."

However, Dr. Rich questioned the validity of that measure, particularly as a primary endpoint. He said it could be that the approved PAH drugs make people feel better but die sooner, as some other cardiology drugs, such as milranone, have been shown to do, "(These drugs) do ***not*** restore normal 6MW. I question whether they were clinically meaningful…In a COPD study, they found that a difference of 54 meters was necessary for the average patient to be improved or worse."

**Measures of Current PAH Therapy**

| Measurement | Improvement achieved |
|---|---|
| Exercise | Up 30-50 meters |
| Functional capacity | 20% - 40% |
| Hemodynamics | Down 2% - 6% |
| Quality of life | Suboptimal |
| Survival | Up ~ 25% |

Dr. Rich also questioned whether any benefit in 6MW at 12 weeks is indicative of any continuing benefit from the drugs. He suggested the drugs should be tested for a year to see what benefit there is at that point, "You can get an initial improvement at three months (with Sanofi-Aventis's beraprost), but it failed to produce a sustained clinical benefit over a significant time frame (1 year). So that raises questions about all the approved therapies…Last year, an Italian group of epidemiologists found that changes in 6MW were not predictive of a survival benefit, and an overview (of current drugs) failed to show a significant survival advantage or a meaningful benefit from these drugs…The current trial designs based on 6MW are flawed."

He urged researchers to validate endpoints for PAH trials – and to make the trials long. He said, "My personal opinion is there should never be another randomized trial of 16 weeks using 6MW…(The answer) is not to beat up on regulatory authorities or criticize the companies…but we must demand that the future trials in which we participate adhere to the highest possible scientific standards. It is okay to say no if you are approached to participate in a trial, and you don't like the endpoints. I think, as an academic community, we need to do that more."

**Performance of IV PAH Drugs on 6MWD ***

| Measurement | Improvement from baseline in 6MWD | % improvement |
|---|---|---|
| GSK's Flolan | 31 meters | 10% |
| Flolan in sickle cell disease | 46 meters | 17% |
| Remodulin IV | 10 meters | 3% |

*Source: Dr. Rich lecture

## CURRENTLY-APPROVED ENDOTHELIN ANTAGONISTS FOR PAH

### GILEAD'S Letairis (ambrisentan)

The FDA mandated monthly liver enzyme testing with Letairis – just as is required for United Therapeutics' Tracleer (bosentan) – as well as pregnancy testing for women of child-bearing age, but European regulators only require liver testing for Tracleer, not Letairis. Does this give Letairis a commercial advantage over Tracleer in Europe? European doctors were uncertain.

**U.S.:** Doctors said the change in the Letairis label to better characterize the fluid retention (edema) has not impacted their view of the drug or their willingness to prescribe it. Those who have tried it all said the results have been good. However, most doctors questioned have not yet tried Letairis, and some were not even aware of it. All said they are (or will) use it for some newly diagnosed patients in order to get a better feel for it, but they agreed that they would not switch patients from Tracleer to Letairis. They were completely unable to give estimates of where usage might be in a year.

So far, these doctors have not seen any elevated liver enzymes (LFTs) with Letairis, but they pointed out that their experience is still limited.

**Europe:** None of the doctors questioned have tried either Letairis or Thelin yet, and most non-academics were not even aware of any endothelin antagonist except Tracleer. Asked if not having to do liver testing in Europe with Letairis, as is required with Tracleer, would influence their decision to try Letairis in the future, doctors were divided. Half said the liver

testing was a non-issue, especially for patients who are coming to the office frequently anyway, and the other half said it would have ***some*** appeal.

## CURRENTLY-APPROVED PROSTACYCLINS FOR PAH

### UNITED THERAPEUTICS' *IV* Remodulin (treprostinil) – switching easy and improves quality of life

Dr. Omar Minai of the Cleveland Clinic presented a poster on the results of a 10-patient study on rapid switching from GlaxoSmithKline/Myogen's Flolan (epoprostenol) to IV Remodulin. He cited several advantages to IV Remodulin: longer half-life, stable at room temperature so it doesn't require refrigeration, and comes in a pre-mixed form. He said the efficacy of Remodulin on functional class and 6-minute walk have been shown, but the study was done to see if there is an improvement in quality of life and patient satisfaction with switching to IV Remodulin.

All the PAH patients in the study had been stable on epoprostenol for one month and clinically stable for 3 months. Patients were then switched from their epoprostenol dose on a 1:1.2 basis to IV Remodulin. Functional class was assessed at baseline, 4 weeks, and 8 weeks. He said they found that quality of life improved significantly with the switch, and patient satisfaction was improved, "All patients tended to have significant improvement and were very happy with (IV) Remodulin. The (patient) diaries also showed patients spending 1.5 hours per week less on drug changes. Symptoms were pretty much the same, and 6-minute walk did not change significantly…Based on this, short-term rapid switching of epoprostenol to IV treprostinil is safe, and the effects are there for at least the first 8 weeks…Patients remain stable for the first 8 weeks...This therapy (IV Remodulin) has the potential to improve quality of life, let patients spend less time on medications, and improve patient satisfaction."

Dr. Robert Naeije of Belgium insisted that the dose of treprostinil has to be doubled or even tripled in going from subcutaneous Remodulin to IV Remodulin, which is different from Flolan, where the IV dose is the same as the subcutaneous dose. An expert from Columbia University said, "We transition, and then adjust the (Remodulin) dose to maintain stability…It (the conversion factor) has been very variable…It is a very safe procedure to do, you can do it rapidly, and it dramatically improved quality of life in these patients, particularly for children. But I think each patient is individual… What is the right dose for a patient? Equivalence is very variable, and you have to work it out with a patient." Dr. White said, "We've had fantastic results with the switch (to IV Remodulin)…I find the dose is in the 2:1 neighborhood. Universally, patients have been happier with (IV) treprostinil than epoprostenol."

*Asked about the incidence of sepsis with IV Remodulin*, Dr. Naeije said, "You have to be careful how you handle the drug. In those few cases (of sepsis), people were, I think, a little sloppy (in handling it). There have been a few more (cases), and it has occurred in more than a few centers, but it is not the drug or the vials. I think it is a sterility, a training issue."

## PROSTACYCLINS IN DEVELOPMENT FOR PAH

### UNITED THERAPEUTICS' *oral* Remodulin (treprostinil, UT-15C SR) – good PK data

A PK poster was presented that offered a preliminary analysis of a subset of PAH patients from the ongoing Phase III trials. The PK study reported on the 38 patients, from three sites only – University of Rochester, University of Iowa, and the University of California, Davis – of a planned 60 patients. All of the patients had been on oral Remodulin for at least four weeks in the open-label, Phase III trial before entering the PK study. Various doses of oral Remodulin (2 mg-16 mg) were administered twice a day with a meal.

The principal investigator of the PK study, Dr. White said, "The PK profile is better than what we expected…I think we will see good efficacy in the Phase III trials."

The key findings in the oral Remodulin PK study were:

- **For doses <10 mg:** All but one patient was within or above the plasma level considered therapeutic (equivalent to a parenteral Remodulin dose of 10-30 ng/kg/min) within 1-2 hours and remained in that range until about Hour 8. By Hour 12, serum levels of treprostinil in most patients were below the therapeutic range.
- **For doses >10 mg:** As with lower doses, patients quickly got in or above the therapeutic range (equivalent to a parenteral Remodulin dose of up to 90 ng/kg/min), but the effect rose more steadily than with lower doses, then started falling off at Hour 6 and fell steadily, dropping below the therapeutic range by Hour 12 or somewhat earlier.
- The PK study patient with the worst response was at 11 mg and has scleroderma. Dr. White speculated that the patient's gut may not work well, but he said that other scleroderma patients have responded to oral Remodulin, so it does not appear to be an interaction of the drug and scleroderma.
- The patient with the highest response was on 16 mg oral Remodulin monotherapy at the time but is now on a combination of Letairis, sildenafil, and oral Remodulin.
- There were no data on trough levels, but a trough walk is being measured in at least some patients in the Phase III monotherapy trial at 11 hours.
- The peak Remodulin serum level for most patients is at about 6 hours. The 6-minute walk test in the Phase III trials is done 3-6 hours after dosing, so patients should have good serum levels, if not optimal levels when tested.

- The Remodulin dose correlated with $AUC_{0-12}$ and $C_{max}$, indicating a linear relationship between dose and exposure.
- The PK profile appeared consistent regardless of PAH etiology (idiopathic PAH vs. associated PAH) or background therapy.

The PK study investigators did not report on any adverse events in the PK study patients. Dr. White said that was because the Phase III trials are still ongoing, but he added that no PK patients have discontinued their Phase III trial. He added, "Adverse events at experienced centers become acceptable over time. Over time, the patients on subcutaneous treprostinil develop tolerance (to the side effects). There is no reason not to think that would be the same with oral treprostinil." The expected adverse events are headache, nausea, flushing, jaw pain, and extremity pain.

*Is there a correlation between plasma levels and symptoms?* Dr. White would only say, "I think the Phase III trials will answer that."

*Will adequate serum levels of oral Remodulin translate into clinical benefit?* Dr. White said he thinks it will as long as the plasma levels are in the range he found in the PK study: "My personal experience with subcutaneous treprostinil is that when you achieve a serum level in the range of 30-50 ng/kg/min, patients get better…More than 30 ng/kg/min is where you need to be to be therapeutic." A company official said subcutaneous Remodulin showed ~18 meter improvement in the 6-minute walk in its pivotal trial (without pushing the dose); IV Remodulin was approved based on bioequivalence, but a study showed ~80 meter improvement when the dose was pushed. In the Phase III trials of both oral and inhaled treprostinil, the primary endpoint is the *median* (not mean) change in 6-minute walk.

*Can oral Remodulin be given with other PAH agents?* Currently, most PAH patients are treated with (1) Tracleer or Letairis, (2) sildenafil, or (3) a combination of Tracleer or Letairis plus sildenafil. A study presented at ATS in 2007 showed some adverse event interaction of oral Remodulin with 125 mg BID Tracleer and 20 mg TID sildenafil, but Dr. White said, "This (PK) study shows no interactions, so it must be a second messenger effect further downstream (that caused the adverse event interactions)."

*Will BID dosing be sufficient?* Most patients in the PK study dropped below the desired range by 12 hours, raising the question of whether dosing every 8 hours (Q8H) would be better. Dr. White said, "That will be answered in the Phase III trials. Maybe being in the (desired) range for 8 of 12 hours is enough. Maybe being continuously in range isn't necessary."

*Asked if oral Remodulin could be dosed TID,* Dr. White said, "We've had this discussion (with the company). If we have to dose TID, some in the company would be very sad, but we could do it."

*Will each patient need to be titrated individually?* "Absolutely," Dr. White said, adding, "Doctors will have to be more sophisticated with oral treprostinil than with the pump. Finding the right dose will be harder for doctors, even though the drug will be easier for patients. Some automated PK kit may be useful (e.g., a modified, in-office, four-hour PK study) …I think dosing variability will be greater with oral than subcutaneous (Remodulin)." Dr. White noted that he currently is slowly increasing the subcutaneous Remodulin dose in all patients.

Another investigator noted that oral Remodulin must be titrated slower than the company initially planned. He said, "We started too high (with too high a dose) initially, and now we are finishing (the trial) with a lower starting dose."

*Asked how he would use oral Remodulin if it were approved*, Dr. White said, "If the oral (treprostinil) is highly effective, most of my patients would choose the oral. It would not surprise me if individual patients had swings in their adverse events during the day – higher at some times, lower at others (e.g., peaks of nausea that come and go). I have 30 patients waiting to switch from subcutaneous treprostinil to oral…A switching study will have to be done when we are closer to completing Phase III."

Data from the first of the three ongoing Phase III trials should be available before the end of 2008, perhaps at the European Respiratory Society meeting in Berlin in October 2008. However, company officials would not speculate on when and where the data will be presented. Ongoing trials include:

- **FREEDOM-C**, the Phase III TDE-PH-301 ("301-C") combination therapy trial of BID oral Remodulin (0.25-16 mg) added to background therapy of oral Tracleer, Letairis, sildenafil, or a combination of these drugs. This randomized, 16-week trial is fully enrolled with 351 patients.
- **FREEDOM-M**, the Phase III TDE-PH-302 ("302-M") monotherapy trial of BID oral Remodulin in treatment-naïve patients. About 80% of the planned 150 patients have been enrolled.
- **TDE-PH-304**, the open-label extension study for patients completing the FREEDOM-C and FREEDOM-M trials.
- **TDE-PH-305**, a 60-patient, hemodynamic study.
- **PK study** is continuing.
- **Biomarker and genetic substudy.** Background blood values are being measured at baseline and after 12 weeks of treatment.

The primary endpoint in the Phase III trials is improvement in 6-minute walk, and the company is expecting an improvement of 20-40 meters. Dr. White said, "I thought we could get 40-50 meter improvement with triple therapy when I started the (combination) trial…If we get a 70-80 meter improvement in 6-minute walk with monotherapy (which is comparable to

subcutaneous treprostinil), why not use oral treprostinil first line? Because bosentan is easier to take."

**UNITED THERAPEUTICS' Viveta (*inhaled* treprostinil) – statistically significant effect but clinical significance questioned**

Viveta has a longer half-life (>3 hours) than Actelion's Tracleer, so it is administered less frequently, and the inhalation time is shorter. The delivery device is the Optineb, an ultrasonic nebulizer.

The results of the randomized, double-blind, placebo-controlled, 235-patient, pivotal, Phase III trial for Viveta, TRIUMPH-1, were presented at ATS, and the trial met the primary endpoint (6MWD), with statistically significant findings. Viveta significantly improved 6MWD, NT-proBNP levels, and quality of life. But Viveta did not have a significant effect on the signs and symptoms of PAH, dyspnea score, NYHA functional class, or clinical worsening.

The results did not impress some cardiologists, who questioned the clinical meaningfulness of a 20 meter improvement in 6MWD. While they agreed that the results are probably sufficient for FDA approval, they weren't sure what the clinical utility would be. A U.S. cardiologist said, "The 6MWD was about 20 meters, and trials of other drugs have shown a 15-40 meter difference. There is a signal of benefit with inhaled treprostinil, but whether that is clinically meaningful is a question. I hope the FDA will require another measure (before approving it). I think the FDA is moving away from 6MWD in short-term trials in favor of improvement in clinical worsening or something clinically meaningful like functional class change – or something event-driven, with mortality or a hemodynamically significant change. Longer trials are needed, and I think the FDA is getting behind that."

On the one hand, an expert explained, Viveta will offer a somewhat more convenient dosing alterative, which is likely to appeal to patients, and trying it before Ventavis might make sense. On the other hand, he said that PAH patients do not necessarily have enough time in the course of their disease to experiment; they need the best drug first, and his view was that Viveta appears inferior to Ventavis. Dr. Vallerie McLaughlin – a cardiologist, director of the Pulmonary Hypertension Program at the University of Michigan Medical Center, and the principal investigator in TRIUMPH-1 – said, "Even though the overall response was (an improvement vs. placebo of) 20 meters, a third had improvements greater than 50 meters…We see that all the time in practice. You try one thing, and the patient doesn't do well, and we try something else."

In the TRIUMPH-1 trial, patients had 4 inhalation sessions per day of 6 µg per session. At baseline, these were patients with a 6MWD of 200-450 meters on oral monotherapy (either Tracleer or sildenafil), and all patients continued that background therapy during the trial. The statistical analysis imputed a Missing Week 2 6MWD test and used LOCF for patients who discontinued for adverse events or withdrawal of consent.

Questions were raised about the use of ***median*** 6MWD rather than mean, but United Therapeutics officials defended the use of median, saying that has been the standard in this kind of

**TRIUMPH-1 Results of Inhaled Viveta**

| Measurement | Viveta n=115 | Placebo n=120 | p-value |
|---|---|---|---|
| **Baseline** | | | |
| On Tracleer | 67% (av. 51 µg/day) | 73% (av. 52 µg/day) | --- |
| On sildenafil | 33% (av. 49 mg/day) | 27% (av. 49 mg/day) | --- |
| Completed therapy | 89% | 92% | --- |
| Discontinued for disease progression | 3% | 0 | --- |
| Discontinued for adverse events | 6% | 3% | --- |
| **6MWD (*median* change over placebo)** | | | |
| Day 1 | 6 meters | --- | Nss |
| Week 6 | 19 meters | --- | <0.0002 |
| Week 12 at trough exposure* | 14 meters | --- | p<0.01 |
| ***Primary endpoint:*** Week 12 at peak ** | ~20 meters | --- | p<0.006 |
| **6MWD at Week 12 (*median* change from baseline)** | | | |
| >20% | 52 meters | 2 meters | --- |
| >30% | 43 meters | 28 meters | --- |
| >40% | 37 meters | 17 meters | --- |
| >50% | 31 meters | 12 meters | --- |
| **Other efficacy results** | | | |
| Borg Dyspnea scale (shortness of breath) | --- | --- | Nss |
| NYHA Functional Class | III | III | Nss |
| No clinical worsening | 97% | 95% | --- |
| Death | 0 | <1% | --- |
| Transplantation | 0 | 0 | --- |
| PAH hospitalizations | 3% | 4% | --- |
| Quality of life: MLWHF global score | Down 4 | --- | <0.05 |
| Quality of life: MLWHF physical score | N/A | N/A | <0.05 |
| **Adverse events** | | | |
| Cough | 54% | 29% | --- |
| Headache | 41% | 2% | --- |
| Nausea | 19% | 11% | --- |
| Dizziness | 17% | 15% | --- |
| Flushing | 15% | <1% | --- |
| Throat irritation | 14% | 8% | --- |

* Defined as ≥4 hours after Viveta inhalation.
** Defined as 10-60 minutes after inhalation, relative to baseline.

trial. There was also less effect in sildenafil patients than Tracleer patients, but company officials and Dr. McLaughlin all insisted that the numbers were too small to draw any conclusions from that.

Of the 212 patients who completed the 12 weeks in the study, ~200 chose to received Viveta in an open-label continuation study. Currently, ~160 patients are being treated with Viveta, with the longest duration of treatment >2 years.

### *Inhaled* Viveta vs. ACTELION's *inhaled* Ventavis (iloprost) – at least doctors/patients would have a choice

*What are the advantages of Viveta over Ventavis?* Dr. McLaughlin said Viveta has a different mechanism of action, non-overlapping side effects, and easier administration over a shorter period of the day (four times a day). She also noted that there is limited placebo-controlled trial data on the efficacy of Ventavis. A United Therapeutics official said, "I think in day-to-day practice, a longer half-life drug with some effect at trough makes this another attractive treatment option."

Another differentiator could be the inhaler. The Viveta inhaler was described as more user friendly than the Ventavis device, but a new inhaler is on the way for Ventavis. A speaker said the new Ventavis device, which is expected to be available "soon," will "dramatically improve" delivery time (down from ~12 minutes to 1-4 minutes).

*Asked how they would choose between Viveta and Ventavis*, doctors said it was too early to make that prediction, but they were quick to say that a drug that has to be inhaled less often than Ventavis (6-9 times/day) would have a significant advantage, if all other things – safety and efficacy – were equal. Dr. Werner Seeger, a lung expert from the University of Giessen in Germany, said Viveta would also have an advantage if it could be dose titrated, because dose escalations are limited with Ventavis. A United Therapeutics official said there is some dose titration possible with Viveta, but not a great deal. A U.S. cardiologist thought Viveta might improve compliance, at least somewhat, "Patient compliance with inhaled iloprost is 'modest.' We haven't had terrific luck with iloprost compliance."

*Would patients be switched from Ventavis to inhaled Viveta, or would only new patients be put on inhaled Viveta?* Doctors said they are likely to use Viveta for both new patients and patients who aren't doing well on Ventavis, but they indicated they are unlikely to switch patients doing well on Ventavis to Viveta just to simplify administration. Even Dr. McLaughlin said she wouldn't do that, "I didn't say I would switch anything. If a patient is doing well on a drug, I usually leave the patient on that drug. But this is another option."

### MONDOBIOTECH's aviptadil VIP (inhaled vasoactive intestinal peptide) – slow progress but still alive

Biogen licensed the rights to this agent in 2006, but reportedly MondoBiotech is handling the development. Experts at ATS were uncertain about Biogen's current level of interest in this.

Dr. Hanno Leuchte, a pulmonologist from Ludwig Maximilians University in Germany, presented a poster on a study of a single 100 µg dose of VIP in 20 patients with chronic pulmonary hypertension. Dr. Leuchte concluded, "One dose causes some pulmonary selective vasodilation. In patients with chronic lung disease and pulmonary hypertension, there is also some increase in oxygenation…VIP possesses vasodilative properties in the pulmonary circulations, leading to decreased work of the right ventricle…The effect was small. We will need higher doses and acute and chronic treatments in the future, but it is at least a safe treatment. There were no side effects."

**VIP Single-Dose Study Results**

| Measurement | VIP n=20 | p-value |
|---|---|---|
| PAP | Down 5% | <0.05 |
| PVR | Down 7.8% | <0.05 |
| PVR decrease >20% | 6 patients | --- |
| Right ventricular stroke volume | Up 7.3% | <0.05 |
| Gas exchange disturbance | Increased | --- |

A one-year, ~60-80-patient, multicenter, Phase II trial began during ATS. The endpoints are increases in hemodynamics and 6MWD. Patients will be dosed four times a day. Dr. Leuchte said, "I don't see this as monotherapy or a first-line treatment. The Phase II study will be as add on therapy, not in naïve patients." Dr. Seeger called VIP "a very strong vasodilator agent."

## OTHER PAH DRUGS IN DEVELOPMENT

- **Novel delivery methods of prostacyclins** – two that were mentioned but about which there were no additional details were:
  - Liposomal encapsulation of iloprost, which would allow it to be nebulized and released over >24 hours.
  - Biodegradable nanoparticles, that are detergent-free, with adjustable properties, high nebulization ability, rapid biodegradation, and low toxicity.

- **Nitric oxide – BAYER's BAY-63-2521**. In Phase I trials Dr. Ghofrani said this drug was shown to be a "very potent pulmonary vasodilator, but it is not pulmonary selective. The systemic vascular resistance is reduced, but patients tolerated it very well, perhaps because they were able to increase their cardiac output." Dr. Seeger said, "This is a very strong vasodilator. It is not specific, which could be the downside…This is a very interesting agent."

A large, open-label, 12-week, Phase II trial has completed enrollment with 70 patients, and results are expected in the next couple of months. Dr. Ghofrani said the top line data showed very good efficacy. Two Phase III trials reportedly will start soon.

➢ **PDE-5 – LILLY's Cialis (taladafil)**. There were no data on this at ATS.

➢ **PDE-1.** This could be a new pathway to reduce proliferation.

➢ **Tyrosine kinase inhibitors (TKIs) – NOVARTIS's Gleevec (imatinib)**. Dr. Ghofrani said, "There is a good rationale for using drugs out of oncology. Can anti-cancer drugs work in vascular disorders? We found imatinib to be active. This was taken to an (animal model of PAH) injected subcutaneously with imatinib. For the first time, pressure was not only reduced but reduced down to normal. And survival in animals was increased from <50% to 100% in a dose-dependent manner. Is this a rat phenomenon only? No…We used it in a first patient who was already on iloprost, sildenafil, and bosentan and was still progressing…(He added 200 mg Gleevec on top of triple therapy) and he had massive improvement in exercise ability, his functional class changed from 4 to 2, and he is still alive and doing well three years later."

Novartis has initiated a Phase II trial of 200 mg Gleevec on top of standard of care. Recruitment is complete with 72 patients. The last patient visit is expected soon, with results likely by fall 2008. The concern is cardiac toxicity, but Dr. Ghofrani said he thinks that can be handled by monitoring. However, until there are trial data, he discouraged doctors from using Gleevec off label – unless the patient is ***very*** seriously ill and the drug is administered by experienced hands. There also may be ways to modify Gleevec to make it more active and less cardiotoxic, Dr. Ghofrani said.

Other TKIs being studied in PAH include:

- **BAYER's Nexavar (sorafenib).** In an animal model, right ventricular (RV) pressure and RV hypertrophy were significantly reduced. Dr. Seeger said, "This has shown a very strong effect in the lab – almost normalizing RV pressure and hypertrophy." The first Phase Ib trial in 12 patients is underway. The protocol was amended after six patients completed four months, but it is not clear what the change was.
- **PFIZER's Sutent (sunitinib)**, which is approved to treat renal cell carcinoma, **SU-9518, and SU-11657.**
- **ASTRAZENECA's Zactima (vandetanib, ZD-6474)**, which is in Phase III development for non-small cell lung cancer (NSCLC).
- **PLX418.**

➢ **Rho kinase inhibitors.** No details on these were available.

➢ **Serotonin – ERGONIX PHARMA's terguride**, a partial dopamine agonist and a 5-$HT_{2b}$ antagonist. Animal studies have been positive, and a placebo-controlled Phase II trial is recruiting patients, with results expected next year. Just before ATS, the FDA granted it orphan drug status.

➢ **Prostaglandin-$I_2$ ($PGI_2$) – ACTELION/NIPON SHINYAKU's NS-304**. There was no news about this at ATS. Actelion will be responsible for development outside of Japan.

## CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Large-scale COPD trials can be problematic, but Dr. Marc Decramer, chairman of respiratory medicine at the University of Leuven in Belgium, argued that they are necessary. He discussed some of the problems associated with large COPD trials.

1. **Dropouts.** He said dropouts are greater in placebo arms, and in COPD trials, the dropout is selective (not completely random), with the worst patients dropping out first, so the study population gets better all the time. As a result, completers are not representative of the ITT population, the decline of variables over time is under-estimated, and the difference between the active treatment and placebo is under-estimated.
2. **Power.** To show a 15 mL/year decline in $FEV_1$, 90% power, and a 35% dropout rate, then each arm of the trial must have ~1,166 patients, and if the trial is powered for subgroup analysis, 5,000 patients are needed.
3. **Exacerbations.** This has become an important endpoint because it is an important patient event. Problems include the definition (symptom-based or event-based) and blinded adjudication of events. Dr. Decramer recommended patients be left in the study despite premature discontinuation of study treatments.
4. **Design.** If patients with prior use of an anticholinergic are allowed in the trial, it means designing withdrawal periods and makes randomization more difficult. He said future trials probably will need to look at a combination of endpoints, which will further complicate trials.
5. **Comparator.** Dr. Decramer argued that new treatments will have to be compared to an active treatment, not placebo.

### COPD DRUGS IN DEVELOPMENT

Three anticholinergics are in development to compete with Pfizer/Boehringer Ingelheim's Spiriva (tiotropium) to treat COPD:

1. **NOVARTIS/SOSEI's NVA-237.** This long-acting bronchodilator is in Phase II development, with a planned regulatory submission in 2011.

**2. GLAXOSMITHKLINE's** agent reportedly just started a Phase II trial.

**3. FOREST LABORATORIES/ALMIRALL's aclidinium bromide.** The good news is that this ***inhaled*** anticholinergic appears as safe and effective as Spiriva. The bad news is that there doesn't appear to be anything about aclidinium that really differentiates it from Spiriva, except perhaps that patients only need one breath-dose per day of aclidinium, and each dose of Spiriva requires two breaths.

Almirall officials admitted there were no significant differences between aclidinium and Spiriva:

- **No difference in onset of action.** One official said, "We will investigate that further, but at present, we see no difference."
- **Similar adverse events.** He described the side effects as class effects, emphasizing that there were no major cardiac side effects, even on EKG. However, he noted, "Aclidinium is broken down quickly in plasma, so the side effect profile could potentially be a differentiator." The main side effect with anticholinergics is usually dry mouth, but an Almirall official said that hasn't been a problem with aclidinium. He also said there is no taste issue with aclidinium.
- **Similar efficacy.** Asked if the efficacy looks the same as Spiriva, he said, "That's a fair analysis…From an efficacy point of view, we have a drug with comparable efficacy."

*How will doctors choose between aclidinium and Spiriva?* It may be mostly marketing or device preference. An Almirall official said, "It is difficult to say (how people will choose). We will have a different molecule, an alternative. It's important to have more than one product." An investigator said, "It (aclidinium) may have a faster onset, it may have better safety, and it uses a different delivery device, a multidose, dry powder nebulizer. Spiriva uses a single-dose device, though Spiriva is coming out with a new device. Cost will also be an issue. I told the company that they need to differentiate aclidinium."

The user-friendly aclidinium inhaler is already sold in Europe, but it has been modified for the U.S. with the addition of a lock-out mechanism to prevent double-dosing, tamper-proofing, and a pre-filled design (with 30 doses). A company official said they plan to try to get the device and drug approved together. An Almirall official said, "Our device is less complicated to use than the HandiHaler (the current Spiriva device in the U.S.), which you have to load and prime and which isn't multidose…We have a competitive delivery system that is easy for patients to understand and use." He said data on respiratory flow with the new delivery device will be presented at the European Respiratory Society (ERS) meeting in Berlin in October 2008, and data on patient reaction to the device will be presented at a future date.

However, a new device has been developed for Spiriva, the Respimat, and it also is very nice. Respimat uses a high, fine-particle mist to deliver the drug, and a Boehringer Ingelheim official said patients really like that because it is similar to a nebulizer, and nebulizers are very popular. Respimat is multidose (60 doses), but it still has to be loaded, and it is a liquid with a preservative. So, the future could become a battle of the delivery devices.

Doctors questioned about the choice between aclidinium and Spiriva said:

- "The delivery device is important. But so is cost and insurance coverage. Patients would prefer coverage to ease of use."
- "The inhaler and the price will affect my choice. Respimat is easy to use."
- "Cost and safety will decide for me. The aclidinium device is good, but cost will decide in the U.K…The Spiriva Respimat device is good, but I can only use it if a patient can't handle the HandiHaler. The aclidinium device is clever, but patients love Respimat because it is nebulizer-like. A device is not enough to get me to change from what I know (Spiriva)."

At ATS, the results were presented from a prospective, randomized, parallel group, multicenter, dose-finding study in 460 stable moderate-to-severe COPD patients. All patients were dosed QD in the morning for 4 weeks with a multidose dry powder inhaler. In the study, only the two highest doses of aclidinium – 200 µg and 400 µg – were comparable in efficacy on $FEV_1$ to Pfizer's Spiriva, and there was virtually no difference between those doses, so the 200 µg dose was chosen for the Phase III trials. The lower doses were clearly not as good. On Day 1, aclidinium appeared to have a somewhat faster onset of action, but by 2 hours, the $FEV_1$ curves of 200 µg, 400 µg, and Spiriva were almost superimposed. Then, at Day 29, the onset of action was comparable to faster than Spiriva.

**Phase II Trial of Aclidinium in COPD (*ITT analysis*)**

| Drug | Number | *Primary endpoint:* mean trough $FEV_1$ at Day 29 | Peak on $FEV_1$ on Day 1 | Peak on $FEV_1$ on Day 29 |
|---|---|---|---|---|
| Placebo | 64 | Reference | 0.192 | 0.141 |
| Aclidinium 25 µg | 65 | 39 | 0.222 | 0.203 |
| Aclidinium 50 µg | 65 | 36 | 0.250 | 0.245 |
| Aclidinium 100 µg | 69 | 83 | 0.294 * | 0.270 * |
| Aclidinium 200 µg | 66 | 148 | 0.340 * | 0.344 * |
| Aclidinium 400 µg | 67 | 128 | 0.315 * | 0.345 * |
| Spiriva 18 µg (open-label trial) | 64 | 161 | 0.296 | 0.356 |

* $p<0.05$ vs. placebo

An Almirall official said, "200 µg appears to be the maximum effect…but we can't find a maximum tolerated dose, even at 6000 µg."

Other posters presented at ATS on aclidinium included:

- **QT study.** A Phase I study in healthy volunteers, aclidinium doses from 200-800 µg showed ***no QT elevations*** over the FDA's 5 msec threshold. Thus, at doses up to four times the intended therapeutic dose, there was no QT effect, and the cardiovascular profile looked good.
- **Systemic exposure.** A study in 16 healthy volunteers found ***low systemic exposure*** to doses up to 800 µg.
- **PK study.** A study in 16 healthy volunteers, given single doses from 600-6000 µg found clear dose-depending responses. The drug was ***safe and well tolerated*** at doses up to 30 times the therapeutic daily dose. No adverse events were considered treatment-related at doses up to 1800 µg.
- **Bronchoconstriction.** A guinea pig study found inhibition of bronchoconstriction was ***comparable to Spiriva*** and Boehringer Ingelheim's Atrovent (ipratropium), and the duration of action is compatible with QD dosing.
- **Cardiovascular safety.** Studies in guinea pigs and beagle dogs showed an increase in heart rate with aclidinium ***comparable to Spiriva***, though the effect fell off faster with aclidinium. On all other cardiac measures, the two drugs looked nearly identical. An official said, "Since aclidinium has a very, very short half-life, the cardiac risk is minimized."
- **Activity in plasma.** A study of human blood from six healthy volunteers found that aclidinium is hydrolyzed at a faster rate than Spiriva or Atrovent. The hope is that the ***rapid plasma inactivation*** of aclidinium will translate into fewer systemic side effects. This won't be determined for certain until the Phase III data are available. An Almirall official said, "Whatever you can do to have less drug-drug interaction is good, and this class has a relatively low risk of drug-drug interaction. Aclidinium is cleared from plasma very quickly, so it minimizes the risk."

Based on these data, experts predicted that the two Phase III trials, which are expected to be reported later this year, will be successful. The Phase III trials are using the new delivery device that the companies plan to get approved and sell with aclidinium. Both are 1-year, placebo-controlled trials with the same design. The primary endpoint in both is $FEV_1$ at 24 hours after dosing at Week 12 (U.S.) or Week 28 (Europe). Both trials completed enrollment with ~800 patients each. Top line data are expected in 2H08, and the data will be presented at a meeting in 2009. The company plans to file in Europe and the U.S. in 2009.

## Regulatory Issues

FDA officials from the Division of Pulmonary and Allergy Drug Products in the Center for Drug Evaluation and Research (CDER) discussed regulatory issues relating to asthma and COPD drugs at an ATS session.

### Asthma

Dr. Badrul Chowdhury, director of the division, reviewed the safety issues with Genentech/Novartis's Xolair (omalizumab). After Xolair was approved for moderate-to-severe asthma in 2003, the FDA became concerned about post-marketing reports of anaphylaxis. The Agency concluded there was a real safety concern and issued a public advisory in February 2007, then added a boxed warning in July 2007.

The incidence appears to be >0.2% – compared to 0.01%-0.05% for penicillin, 1% for Abbott's Humira (adalimumab), etc. – but the cases can be quite serious. Many have pulmonary involvement, and ~15% have required hospitalization. There is no apparent dose relationship, and while 70% of the events occur within two hours of administration, anaphylaxis can occur days later. Yet, the FDA still feels the benefits outweigh the risks, and a black box is not necessary, but the Agency continues to monitor the situation.

### COPD

A number of companies are trying to develop a new surfactant for the chronic treatment of COPD. The first surfactant was approved to treat acute respiratory distress syndrome (ARDS) in infants. The FDA's Dr. Anthony Durmowicz explained that the requirements for approval of a surfactant in chronic COPD will be quite different, "RDS is not a complicated disease. It is essentially replacement therapy. Drug exposure is short, limiting the toxicity profile to a defined period. The risk:benefit profile may be different for a life-saving therapy like that. Obstructive lung disease (COPD) is likely a functional surfactant difference rather than a deficiency. Pharmacologic doses may be employed rather than replacement. Drug exposure would be much longer, potentially lifelong. The toxicity profile will be different, with chronic dosing and different routes of administration. The risk:benefit profile will be different. And we don't know the long-term risks."

A chronic use indication will require a different, more comprehensive development plan than for RDS replacement therapy, Dr. Durmowicz said. Among the data the FDA will want for any new chronic-use surfactant are:

- **Toxicology.** Dr. Durmowicz said there is very limited toxicology and pharmacologic information on chronic use of a surfactant, even in animals, and not much is known about carcinogenicity and reproductive toxicities.
- **Drug delivery.** A company would need to demonstrate the drug is not degraded in the delivery system – conventional jet nebulizer, "high efficiency" nebulizer, unique delivery device, or dry powder inhalation.

- **Clinical efficacy.** Surfactant products are mixtures of several active drug components, so they will be treated as combination drug products by the FDA, and, as with all combination drugs, the company will have to show the benefit from each component.
- **Study endpoints.** While $FEV_1$ is the typical endpoint used for COPD drugs, Dr. Durmowicz said that may not be appropriate by itself for surfactant-based drugs. The FDA will want to see "direct, clinically-meaningful" endpoints such as reduction in exacerbations, increase in exercise tolerance, and patient-reported outcomes (PROs). Measures of these clinical endpoints will need to be justified and verified (validated).
- **Dose-ranging studies.** There was little or no dose exploration performed during development of surfactants for ARDS, but he said the FDA will require assessment of varying doses in chronic therapy "to determine the appropriate balance between safety and efficacy." This includes finding the minimally effective dose.
- **Trial size and length.** Dr. Durmowicz expects that a chronic indication will require a total exposure of 500-1,500 patients, with 300-600 exposed for at least six months, and 100 for a minimum of one year, though exposure requirements could be more or less depending on the specific indication and the indicated population.

Another FDA official reviewed safety concerns with inhaled corticosteroids, such as GlaxoSmithKline's Advair (fluticasone + salmeterol). She said the FDA expects use of products combining an inhaled corticosteroid with a long-acting beta agonist (ICS/LABA) to increase in the future, so the Agency wants to better understand the safety profile, particularly with respect to pneumonia.

A pneumonia signal was seen recently in long-term COPD studies, and the culprit appears to be the corticosteroid. The FDA has concluded that there is an increased pneumonia risk in COPD patients treated with an ICS alone or in combination with a LABA, and the pneumonia was associated with significant morbidity, though not necessarily death. Patients over age 65 appear to have increased risk. The official said, "We think (even though it is not in the label) that the pneumonia is more of a local effect in the immune system of the lung. We think it will occur with all corticosteroids. It is not a LABA effect; it is an ICS effect. Personally, I expect the same issue with mometasone."

*Will the boxed warning be added to other COPD drugs?* The official said, "There are not enough data to do that, but there currently is class language on pneumonia generally. Advair has more descriptive information. As we get information on the others, we will update their information (on pneumonia)."

*What does this mean for bronchodilator development, particularly combination products?* An FDA official said the Agency will ***not*** require longer (>1 year) or larger trials, "Pneumonia is a risk, not a barrier (to approval)." The FDA ***will*** expect companies to be "more watchful, more proactive, and to use better definitions for pneumonia."

At another session, Dr. Nicola Hanania, director of the Asthma Clinical Research Center at Baylor University in Texas, reviewed FDA draft guidelines for COPD drug development – other than surfactants – in Phase III trials. He pointed out that:

- **Trial design.** The FDA requires placebo-controlled, double-blind, randomized, parallel-group trials:
  - An active comparator is encouraged but not mandated unless the company is seeking a comparative claim.
  - Non-inferiority trials are allowed to use an active comparator, "but companies should be aware there are additional issues to consider when doing this."
  - For a drug to reduce symptoms, patients should have measurable symptoms.
  - Multiple doses may need to be tested.
- **Primary endpoint.** The FDA still recommends a single primary endpoint, with supportive secondary endpoints if the efficacy is robust. European regulators, on the other hand, want two primary endpoints ($FEV_1$ and SGRQ). FDA-acceptable primary endpoints include:
  - $FEV_1$, studied serially, even though this can correlate poorly with patient outcomes.
  - Clinically-meaningful symptom relief, but the Agency has not defined what it means by clinically meaningful. "Symptom scores should not be used alone, and they must be validated. For example, BDITDI are less compelling than validated patient-related instruments. The FDA also does not like measures administered by third-parties. MRC is not a good measure of a new drug. An increase in TDI has been demonstrated vs. placebo, but it may be confounded by cardiac measurements. Dyspnea scales (CRIO and VAS) are commonly used. Patient-recorded outcomes (PROs) – SGRZ, CRQ, SF-36 – can be used, but they have limits."
  - Modifying or preventing exacerbations. "This endpoint needs to be shown to be clinically meaningful. No biomarker of exacerbation or severity exists at present that can be used in a randomized trial."
  - Altering disease progression, shown through serial $FEV_1$.
  - Modifying lung structure.
  - Mortality is the best possible measure, but determination of the correct cause of death is important, and mortality is not an endpoint the FDA is currently seeking in COPD trials.
- **Secondary endpoints.** These should be chosen to support the primary endpoint. "No biomarkers are available to establish efficacy of a COPD drug. Six-minute walk can be used, but the problem is there is no clear recourse

on what the clinical utility is. The EMEA has turned down a 45 meter improvement as the minimum."

- **Inhaled drugs.** The device cannot be changed in Phase III.
- **Combination trials.** These must show the efficacy of each component. Here, two primary endpoints may be used.

*Asked about the use of FVC as a primary endpoint in COPD trials*, Dr. Hanania said, "That is a good endpoint. It is reproducible if done properly. It may reflect lung volume better than $FEV_1$, and it may be more significant. The FDA wants both $FEV_1$ and FVC. Neither the FDA nor the EMEA allow the use of only FVC as the primary endpoint in COPD. You need to show a minimum 100-140 point change in $FEV_1$."

Officials of two companies that sell devices for measuring lung performance agreed that FVC is a poor endpoint in COPD. One explained, "Different technicians do FVC differently. The National Health Lung Education Program is adopting the $FEV_1/FEV_6$ ratio in lieu of FVC." Another official said, "FVC is more effort-dependent."

## IPF

*Is FVC an appropriate (and FDA-accepted) endpoint for IPF trials?* Experts all agreed that it is. One said, "Serial FVC predicts mortality in patients not desaturating <88% in the 6-minute walk test (6MWD). However, the experts haven't yet convinced the FDA of this. An FDA official said the endpoint the FDA wants to see in IPF trials is ***mortality***, not FVC, "A sponsor could use FVC, but they need to show the effect on mortality…And mortality does have to be better than the comparator. Whether it needs to just show a trend or be statistically significant depends on the other data." The official said that, theoretically, FVC could be the primary endpoint as long as mortality was measured and showed at least a trend to improvement.

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