Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Intermune impressed doctors with the significant survival benefit in a subgroup analysis of its Phase III trial of **Actimmune** (interferon-γ), even though that drug failed its primary and secondary endpoints. Pfizer and Boehringer-Ingelheim were aggressively and successfully marketing their new COPD treatment, **Spiriva** (tiotropium). New data was presented on the antimicrobials, telithromycin (Aventis's **Ketek**) and moxifloxacin (Bayer's **Avelox**), but there was little excitement about either of them.

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The meeting focused on chronic obstructive pulmonary disease (COPD), asthma, pneumonia, bronchitis and idiopathic pulmonary fibrosis (IPF), with little attention focused on rhinitis.

INTERMUNE's Actimmune (IFN-g)

Partial Phase III data from the GIPF-001 study on Actimmune was presented twice at the meeting, first at a company-sponsored symposium, and then in a general session. The data showed enlarged somewhat on what had been in the company's press release earlier this month – that the trial failed all the primary and secondary endpoints, but that there was a very significant mortality benefit in a subset of mild-moderate patients but no benefit in patients with severe disease.

Interestingly, the company used different definitions of mild-moderate idiopathic pulmonary fibrosis (IPF) in the press release and in the presentation at ERS. Using the press release definition of forced vital capacity (FVC) >55%, there was a 70% improvement in mortality with Actimmune compared to control. Using the FVC>60% definition at the meeting, there was a 74% reduction in mortality with Actimmune. Perhaps most compelling was the company's graphic representation of the reduction in mortality at the range of FVC. A researcher explained this change: "We did a regression analysis to look at the data in a way that was not manipulating the intent-to-treat (ITT) analysis, and if you look at it from FVC>55%, the mortality data is significant, but that will be criticized because it is a subset analysis (80% of pts), so I think a regression analysis is a more powerful way to look at it…And the more you look at the data, the better it gets."

The speaker also emphasized that the data appears to be stronger the longer patients are on Actimmune. That is, the response lines appear to separate after 48 weeks and keep separating out to 72 weeks. He said, "At 48 weeks there was no difference in the dyspnea index, but at 72 weeks there was a big difference (p=.017), suggesting that patients had a demonstrable difference in dyspnea after 48 weeks of IFN-γ. It suggests that patients benefit from getting the drug when FVC is preserved or at an earlier stage of the disease. There also was a suggestion that patients have a better chance of staying off oxygen with IFN-γ. The question to the steering committee was how to look at this data in such a way as to take into account what appears to be an effect on survival based on baseline FVC – how to look at FVC in a way that doesn't slice and dice and includes the entire intent-to-treat group."

Another expert described the Phase III trial as, "well-matched," saying it is the best study done so far in IPF. He commented, "It is remarkable how well the

patients stayed in the study and how well they took the drug…Time to confirmed FVC progression took a lot longer for IFN-γ patients, but that was not statistically significant. It looks like the break point is 48 weeks or somewhere thereafter. At about 48 weeks the two groups tend to diverge in the dyspnea index, with placebo worsening and IFN-γ stable or improving...Placebo patients tended to have more need for oxygen over time, and treated patients tended to stay the same or have less need for oxygen.

There were 330 patients (age 20-79) in this trial, randomized to either Actimmune (200 µg TIW) plus prednisone or prednisone alone. The data cutoff for analysis was 48 weeks after the 306th patient started treatment. The data was unblended, but not the patients, and the trial is continuing. Once the trial is complete, there will be open label access to the drug for all study patients. Patients were eligible for this trial if they failed to respond to steroids, had worsening disease over the past year, and had HRCT with definite or probably IPF. The primary endpoint was progression-free survival, defined by death or physiologic disease progression, powered to show a 50% reduction, but on an intent-to-treat analysis, there was a only a relative reduction of 11% (p=.53) with Actimmune.

Actimmune was generally well-tolerated. Side effects were higher than in the control group, but the differences were not statistically significant except for pneumonia. A researcher said the pneumonia was not a concern because there was no excess mortality. He said he believes the pneumonia and other side effects were simply picked up more frequently in the Actimmune patients because IFN-γ causes an inflammatory response, which makes the symptoms worse or more noticeable. Pneumonia, he said, is difficult to diagnose definitively in IPF patients, "Because the pneumonia is more noticeable in the Actimmune patients, it may be picked up more frequently. It may be there in the control patients as well but not picked up because they are less symptomatic." Another expert said, "It is unknown if the flu-like symptoms improve over time, but since a high number of patients stayed on the drug, I assume the symptoms lessened. Why there was more pneumonias but the same number of deaths remains to be explained….There was an excess of non-fatal pneumonia… It is interesting why that happens. The company will go back and see what doctors meant by 'pneumonia.'"

Actimmune Phase III results

Measurement	Interferon-g n=162	Control n=168
Demographics		
Age	64	63
Male	71.6%	65.5%
Caucasian	91.4%	86.3%
Current smoker	4.9%	8.9%
Prednisone use at baseline	75.3%	77.4%
Supplemental oxygen use	40.7%	41.0%
Median days from initial IPF diagnosis	329	295
Study Compliance		
Received study treatment	100%	100%
Discontinued treatment (though some stayed in study)	20.4%	16.1%
Discontinued study	12.3%	8.3%
Death	9.9%	16.7%
Findings		
Death or disease progression (ITT analysis)	46.3% (nss)	51.8%
Death in patients with Baseline FVC>60%	3.3% (n=90, p=.02)	13% (n=92)
Death in patients with Baseline FVC≤60%	18.1% (n=90, p=.75)	21.1% (n=92)
Death in protocol-eligible patients	8.1% (p=.055)	15.7%
FVC change from baseline	-4.7%	-3.3%
Response status		
Improved	3.1%	4.2%
Same	71.0%	70.2%
Worse	25.3%	24.4%
A-a gradient mean change from baseline	3.3 mmHg	2.9 mmHg

Actimmune Phase III Side Effects

Side Effects	Interferon-g n=162	Control n=168
Serious AE	34.6%	30.4%
Discontinued treatment due to AE	4.9%	1.2%
Fever	32.7%	9.5%
Flu-like illness	19.1%	7.7%
Headache	52.5%	29.8%
Serious respiratory infection	16.7%	8.3%
Pneumonia	11.7% (p<.05)	4.8%
Fatal respiratory infection	1.9%	1.8%

An investigator-sponsored study of Actimmune in 27 symptomatic, newly diagnosed IUP-IPF patients in Greece and the U.K. compared 200 µg IFN-γ (given subcutaneously three times a week) to 1 mg/day of colchicine. This trial excluded end-stage IPF patients. At 11-month follow-up, the researchers found that patients did better on IFN-γ than colchicines, but survival data was not available. There was no statistically significant difference between the two groups in terms of FVC, TLC, or PO2, or cough at six months, but there was less dyspnea with Actimmune. Additional data from this trial on the effect of IFN-γ on growth factors will be presented at the American Thoracic Society meeting in Seattle in May 2003.

IFN-g vs. Colchicine

Results	**IFN-g**	**Colchicine**	**p-value**
Death	6% (1 patient)	33% (3 patients)	p=.0955
Improvement at 6 months	59%	0%	p=.0037
Stable disease	18%	23%	p=.3360
Worse disease	24%	77%	p=.0111
Dyspnea	.035	.548	p<..05

A prior, Phase II trial of Actimmune, referred to as the Vienna study, was not placebo controlled, but the long-term results have been positive. These were steroid-resistant patients with mild disease, and most treated patients stayed the same or got better, while control patients stayed the same or worsened.

During a panel discussion of the Phase III Actimmune data, several pertinent questions were posed:

- **Could the higher response in mild-moderate patients than in severe patients have been due to concomitant emphysema?** The presenter said, "If preserved FVC is measure of early disease, then the data holds. Right now we don't have data on previous smoking. That is something (another expert) thinks is a very important part of the analysis. We don't have that data, but we will. But based on the CT scans, there was not a lot of emphysematous changes by CT. However, that could be a confounding variable."

- **Why were steroids successful in 25% of patients?** An IPF expert said, "Probably those patients didn't have IPF."

- **What should we do going forward with patients with severe IPF?** An IPF expert said, "Maybe it is of less value, but the jury is not completely in yet." Another expert said, "The effect, if any, is in mild IPF, and not severe IPF, "The data suggests to me that if you use (Actimmune) in milder cases, maybe there is an effect. A Mayo Clinic study of 17 severe patients who didn't qualify for the (Actimmune) study found no patients who responded, and 35% died within a few months. So severe patients are not helped with the drug. (Another researcher) also looked at 33 terminally ill IPF patients treated with (Actimmune), and none improved. So, severe disease is not likely to respond to this therapy."

Other questions likely to be raised by this data include:

1. **Patient demographics**. Demographics for the regression analysis patients was not provided, but should be available at the Chest2002 meeting November 2-7, 2002, in San Diego. Of particular interest will be:
2. **Age of the patients.** Patients age <60 generally have longer survival than patients aged >60.
3. **Type of IPF.** NSIP has a much lower mortality rate than IUIP.
4. **Smoking history.**
5. **Trial blinding**. *Did the adverse events in effect unblind the trial?* A researcher said, "Many IRBs raised that question. It has been my experience -- and I spoke to others – that we really can't tell who is getting the drug. In off-label use, some patients have flu-like symptoms and many do not. About 30% of patients have flu-like symptoms." Another IPF expert said, "It is clear from retrospective inquiries that patients had no idea if they were on drug or not."
6. **FDA and European approvability**. A leader in the IPF field said he believes Actimmune is FDA-approvable because this is a fatal disease with no other good therapies. Another expert said, "The company will need another trial, possibly a two-year trial, for EU registration. If Intermune rushes this (into the regulatory process), and it fails, then it will take even longer to get it approved in the EU and the U.S."
7. **Length of the study**. The drug appeared to show more effect after 48 weeks, so perhaps a two-year trial would be better.
8. **FVC cutoff**. Should it be FVC>55% or >60%?
9. **Feasibility of additional trials**. *Should – or even can -- another trial be done in patients with FVC>60%?* An IPF expert said, "As Winston Churchill said, this is not the end, just the beginning…You could suggest that the (Actimmune) survival data is such that you can't do another placebo-controlled trial, but I think you could argue it either way." Several doctors commented that it may be difficult to get doctors, hospitals and patients to do another trial if it means denying Actimmune to patients, but other experts disagreed, insisting that it will not be too difficult to find patients for another trial. One said, "I don't think it will be impossible or unethical to do another Actimmune trial, and the company is committed to another trial." Two other U.S. experts said they believe that patients can be recruited for a new trial, and they indicated their sites would be willing to participate.

   Indeed, a European study is due to start soon, though the design is not yet finalized. One expert said any new trial should use falling FVC as a cutoff, not a percent of FVC. Another expert is recommending the company use an FVC >50%, not 55% or 60%. He said he would be willing to enroll patients in another trial, and suggested these possible designs:

   - All patients get the drug.
   - 2/3 of patients get the drug, a 2:1 randomization.
   - Actimmune compared to standard therapy of prednisone + a cytotoxic (azathioprine, methotrexate or cyclophosphamide).

Intermune officials said they will be meeting with the FDA to show the agency the Actimmune data and judge the agency's response/reaction. Intermune is expected to submit Actim-

mune for FDA approval only if the agency indicates the mild-moderate mortality data might be sufficient for approval. If the FDA has problems with the data or suggests another trial will be necessary, the company probably will do an additional trial before submitting its drug to the FDA. Intermune reportedly wants to avoid a non-approvable letter, which would be likely to have a negative impact on reimbursement. Officials indicated they do eventually want FDA approval because, even though most private insurance covers off-label use of Actimmune for IPF, Medicare will not reimburse for it unless it has FDA approval.

A senior FDA official offered some comments that may shed light on the agency's likely approach to this drug. He spoke in a general way about the approvability of a drug for a fatal condition with no currently approved therapies if that drug's pivotal trial failed to meet its primary or secondary endpoints. The official's responses make it appear unlikely but not impossible -- that Intermune can gain approval for Actimmune without an additional trial.

QUESTION 1: Could a drug be approvable if it shows a statistically significant benefit (or even a dramatic benefit) in terms of reducing mortality based on either an analysis of the primary endpoint or secondary endpoints?

ANSWER: "There is provision in FDAMA for basing approval on a single well-controlled study 'with confirmatory evidence.' We wrote a guidance on when we might do this, and said we might if the study was statistically very persuasive, consistent internally, multi-center, etc. We also said the case for doing so usually involves outcomes where doing another trial would create ethical difficulties, which would be the case if a drug showed a nominally significant effect on an important endpoint in a disease with no treatment. Generally, that would mean that the trial showed an effect on mortality or an important morbidity (e.g. stroke). Usually, mortality, if successfully reduced, would have been an identified endpoint, and we certainly pay attention even if death was a secondary endpoint."

QUESTION 2: Can a drug for such a serious condition be approved based on secondary endpoints alone?

ANSWER: "Ordinarily, secondary endpoints are not considered unless an effect on the primary endpoint is shown. There could be cases in which we thought the specified primary endpoint was silly or poorly chosen, and use another, but this is quite unusual."

QUESTION 3: If the patients were divided into 2 groups: (a) mild-moderate and (b) severe -- for analysis purposes -- and there was a dramatic benefit in just one of these subgroups, could it be approvable?

ANSWER: "If the two groups were pre-specified, and statistical analyses were planned to take into account the multiple endpoints, an effect in one group (either the more or less severe) might be sufficient, but note that there usually need to be two studies."

There are two lessons from the Actimmune trial, another source said:

1. If you wait too long, nothing works, even IFN-γ.
2. You can't treat patients for a short time and see an effect in the population or in an individual. Long enough might be six months or more.

An American Thoracic Society (ATS) consensus statement on IPF therapy was issued in 2000, and it recommends combined therapy with steroids and either azathioprine or cyclophosphamide. That consensus statement is due to be re-written soon, but a member of the panel said, "I am struggling with what it should say. The existing ATS statement was a huge battle. We had quite a fight over it, and it will be a monumental struggle to get more out of us until the (IFN-γ) data is published."

In the U.S., there are about 17,000 patients with severe IPF, and about 10% of these (~1,500) are on Actimmune. There are another 33,000 mild-moderate IPF patients, with about 2% of these (~500) on Actimmune. Many U.S. doctors have indicated they intend to use Actimmune in mild-moderate IPF based on this data, and European doctors questioned agreed. Most doctors – U.S. and European -- indicated they will not recommend Actimmune for severe IPF patients, but they will prescribe it for them if pressured by the patients – and if it is reimbursed. For example, one expert who participated in the Actimmune trial said he is using Actimmune off-label, based on FVC and a diffusion capacity <30%, among other things and no longer requires Actimmune patients to be steroid-failures. A U.K. doctor said, "There will be some experimental use off-label in private patients in my country, but no widespread use until there is NHS coverage, and that won't come until it is approved."

An Intermune official admitted the challenge for the company will be to convince internists and primary care doctors to refer IPF patients to a pulmonologist earlier – and the company can't promote off-label use without FDA approval. However, several sources commented that the company is very aggressive, and already has been pushing the off-label marketing envelope.

Yet, there is caution in the medical community over the Actimmune data. One expert (UCSF) said, "What concerns me is that we've seen an initial pattern (of response) like this several times, and that didn't play out. We need more data. We need to complete the study and see the data….I don't want clinicians to not do evaluations and not enroll patients in another trial. It is still too early, and this was only 330 patients." Another (Mayo) said, "We are not convinced of the value of Actimmune and will only prescribe it in a limited manner, mostly if patients insist."

Officials of U.S. managed care companies who were questioned said that they are paying for Actimmune now off-label for IPF, and all plan to continue to do so. Even off-label use of Actimmune by patients with severe IPF is unlikely to be

restricted significantly by most managed care firms. One official said, "There is more opportunity to restrict use in a retail setting, but in a medical office, we rely on the professional activity of the doctor, and we don't put huge pressure on them." Here are their comments in more detail:

➢ One said, "We have recent legislation in our state that goes into effect on January 1, 2003, that requires plans to pay for off-label use of FDA-approved drugs, but it allows us to require some information, such as articles in two peer-reviewed journals...However, **Actimmune probably would not appear on our radar screen unless there was a case with a challenge and a question of patient safety.** The majority of injectibles go through the (reimbursement) system without challenge, so the chance of a review are not good. What plans might do is stop off-label use of something more commonly used, like Johnson & Johnson's Remicade (infliximab), MedImmune's Synagis (palivizumab) or other drugs that are more highly utilized and have more off-label uses. Remicade, for example, has wide off-label use, and it is advertised on TV and the Internet, so we will focus on that, not Actimmune. You have to figure where you have a chance to win the battle and where patient safety is more challenged. You have to pick your battles."

➢ Another said, "**Actimmune is not on the top of our radar screen.** My feeling is that in situations like this, dealing with a critical disease, health plans are not going to intrude on into the patient/doctor relationship. The doctors who are using this are reading the studies, and they will tell their patients the data isn't good and physicians don't want to do harm. Now that the study is out, they will probably tell their severe patients that we really shouldn't use the drug. But we are very careful in our application of prior authorization because our goal is to minimally intrude into the patient/doctor relationship, and we only occupy that space when there is a tremendous consumer advantage -- in terms of significant side effects, demand/management issues, etc., -- and then we will. But Actimmune for IPF doesn't meet our criteria. **If the FDA approves it only for mild-moderate IPF, we would probably issue guidelines but probably not request medical records to make sure or to validate that situation.** I think you have a situation here where doctors want to do the right thing, and a plan may issue some guidance, but I don't envision at this time that we will implement a prior authorization program and required medical records for all the (IPF) patients. Here you have a situation where the mortality is almost assured, and it is a small number of patients, where **it just doesn't make sense for us to tell people what to do.**"

➢ A third said, "**We might set up some criteria and require some pre-authorization for its use.** If the FDA approves it, we will mirror FDA approval and set up our criteria to define what mild-moderate IPF is. If a patient didn't meet the criteria, we would do a second review by a physician to see if there is anything special to allow outside criteria. If Actimmune were not approved by the FDA, we would continue to look at it the way we do now. We would consider this life-saving, and we would still consider covering it. Some employers say they don't cover a drug unless the FDA has approved it, but if we are the decision-maker, we probably wouldn't change except to restrict to patients without severe disease, like transplant refusals. But this is not too low for us to review; we have a low cost threshold ($1,500) for reviewing drugs."

Other IPF therapies in development:

- Intermune's pirfenidone. This could eventually be an add on agent to Actimmune. In hamsters it reduces lung fibrosis, but a Japanese Phase II trial failed the primary endpoint, though most patients' FVC improved or remained stable while the placebo patients worsened. The study was stopped because of a lower incidence of acute exacerbations with the drug (1:74 with drug vs. 5:37 with placebo). There is some photosensitivity with this agent.
- N-acetyl-L-cysteine (NAC)
- Leukotrienes
- Endothelin-1
- Amgen's Enbrel (etanercept), a TNF-α inhibitor
- Novartis' Gleevec (imatinib). Novartis reportedly is considering doing a trial of Gleevec in IPF.

OTHER RESPIRATORY DRUGS IN DEVELOPMENT

Interestingly, the Germany Respiratory Society has issued an official recommendation that patients use the same inhaler for all their respiratory drugs to enable patients to develop a better inhalation technique and to avoid confusion. This makes it harder for single therapy agents that use a different inhaler.

Advair has caught on very well – in COPD as well as asthma -- and sources generally believe it will be hard for other inhaled steroids to market against Advair, though they didn't rule out the possibility. Most doctors were aware of Schering-Plough's Asmanex, but many doctors knew little about Altana's inhaled steroid, ciclosenide, and even less about its PDE-4 inhibitor, roflumilast. A Finish doctor said, "It will be hard for Asmanex and ciclosenide to market against Advair."

ALTANA

(formerly Byk Gulden)

Alvesco, the world-wide brand name for ciclesonide, a dry powder inhaled steroid for asthma. The drug was filed in Europe (UK) in May 2002, and will be submitted to the FDA in spring 2003. The formulation is not a suspension but a solution with very small droplet size.

At an Altana-sponsored press conference, speakers refused to provide many details on the completed Phase III trial, indicating there may be some results presented at Chest2002 in San Diego in November 2002, but most of the data may not

be released until spring 2003. A speaker would only say that the Phase III trial has 600-800 patients, lasted 13 weeks, and compared ciclosenide to budesonide (AstraZeneca's Pulmicort) and fluticasone (GlaxoSmithKline's Flovent). The primary endpoints were FEV, FVC, symptom relief and rescue medication reduction.

Speakers cited several advantages to ciclesonide over other inhaled steroids:

- Equal or better efficacy than budesonide and fluticasone
- QD dosing at 50-100-200 µg, morning or evening, in an MDI inhaler with HFA.
- Fewer systemic side effects than budesonide or fluticasone, **particularly less suppression of cortisol** than other inhaled steroids, even at a high (1600 µg) dose. A U.K doctor said, "If the cortisol data holds up, it could be important."
- Titration possible. The company claims: "The use of inhaled corticosteroids has been limited by the adverse events at higher doses. Ciclosenide may offer an opportunity to extend this boundary."
- Lung activation.
- Greater lung deposition: 52%, compared to 16% for fluticasone MDI, 28% for budesonide MDI, and 51% for BDP HFA MDI.
- Pricing is likely to be lower than for GlaxoSmithKline's combination therapy, Advair (fluticasone propionate 100 mcg and salmeterol 50 mcg), sold as Seretide in Europe.
- Local side effects comparable to placebo and fewer than with other inhaled steroids.

Ciclosenide vs. Other Inhaled Steroids

Side effect	Altana's Alvesco (ciclesonide)	GlaxoSmithKline's Flovent (fluticasone)	AstraZeneca's Pulmicort (budesonide)
Dysphonia (hoarseness)	1.6%	4%-8%	1%-6%
Sore throat	1.9%	10%-14%	5%-10%
Oral thrush	0.2%	2%-5%	2%-4%

Asked if doctors will prescribe ciclesonide monotherapy now that combination therapy with Advair has become so popular, a speaker said, "COPD patients tend to under-use available medications, and only a small percentage of COPD patients take Advair." A U.K. doctor said, "It will be hard to unseat Advair. Symbicort has some advantages, but other inhaled steroids will have a hard time." A U.S. doctor was more optimistic about the outlook for ciclosenide, "If the data holds, it will replace all the inhaled steroids, including Asmanex."

Sources offered three arguments in favor of ciclosenide:

1. **Cost**. An Altana official said, "We are taking a look at the popularity and growth of fixed combinations. We think there is still an opportunity for monotherapy in mild patients, where they could be potentially overmedicated, and the cost of combination therapy is more."
2. **Elimination of need for a beta agonist**. This is a reverse of the negative argument that ciclosenide isn't combination therapy. A researcher said, "The advantage of the combination is the dual mechanism, and there is no need for this with ciclosenide. The need for a beta agonist goes away with ciclesonide. A large number of patients can be just as well controlled on an inhaled steroid alone (with ciclesonide). We also want to take patients to the minimum level of treatment. On the other hand, if a patient needs an additional therapy, an add-on therapy, then there are beta agonist monotherapies available."
3. **Safety in children because of less suppression of cortisol**. Another researcher said, "I think the safety in childhood asthma is important, where combination inhalers are a problem. In the U.S. there is widespread use of leukotrienes because of the fear of inhaled steroids, particularly in children, and this is safest steroid and should be of particular value in children." Altana has begun a trial in U.S. children, but those results will not be available for at least a year.

Roflumilast, a PDE-4 for asthma and COPD that will be marketed by Pharmacia. There was no new data at this meeting, just some posters that were discussed at the company's R&D day. The company declined to discuss why the regulatory filing has been delayed except to say it wants additional data, and that this was not a unilateral recommendation by Pharmacia. Officials would not indicate whether it is additional safety or efficacy data that they are collecting.

Doctors didn't seem to know much about this agent, except that it had been delayed. Most were dubious about the outlook – unless Altana proves to be a very good marketer. Several sources suggested roflumilast would be add-on therapy. A Belgian doctor said, "The roflumilast outlook depends on our experience with Spiriva."

The delay gives Altana's competitors an opportunity, and there are several other PDE-4 inhibitors in development. A Glaxo official predicted that PDE-4s will be approved in the U.S. before Europe because of stricter rules on tissue reversibility in the EU.

Other PDE-4s include:

- GlaxoSmithKline's Ariflo (cilomilast), in Phase II
- Merck's, in Phase II development
- Pfizer's PD-168787, in Phase I
- Schering Plough's D4418, Phase I
- Icos' IC-485
- Glenmark Pharmaceuticals' GRC-3015

ASTRAZENECA'S Symbicort
(budesonide+formoterol)

This combination product is approved in Europe, but several sources said the FDA has had a problem with the variability of the dose with Symbicort delivered in the Turbuhaler, and that has delayed its submission in the U.S. Last year, there had been speculation that Zeneca would license the deliver device Novartis is using for Foradil (formoterol), and that device was well-received by U.S. doctors at an American medical meeting. However, an AstraZeneca official said the company is developing a new device for the U.S. market and will submit a PMA for that instead. The company plans to start a Phase III trial in the U.S., and the expectation is that the new device will be used in that trial.

The marketing advantage of Symbicort – when it is approved, which may not be until 2005 -- is likely to be the ability to adjust dosing or add additional doses during the day, which can't be done with Advair. Several U.S. doctors indicated this could differentiate Symbicort enough to allow it to take market share from Advair, which already is popular and is likely to be strongly entrenched by then.

Most European doctors said they currently split their use fairly evenly between Symbicort and Advair. A German researcher said he uses Symbicort for about 40% of his asthma patients, with 60% getting Advair, "The two drugs are comparable but Advair was on the market first, and it is very popular." A U.K. doctor said, "I use Symbicort and Advair almost equally; it depends on what inhaler the patient already was using. If he was on a Turbuhaler already, then I'll use Symbicort, otherwise, I'll prescribe Advair." A Finnish doctor said, "Symbicort works slightly faster, but the difference is not clinically significant. If a patient was already on a Diskus medication, then I prescribe Advair; if the patient was on a Turbuhaler, then I use Symbicort."

IVAX'S Formoterol

IVAX is working on its own version of formoterol, not in combination with anything else. A source said it would be priced lower, and will utilize a proprietary device similar to the Novartis Foradil device.

NOVARTIS/GENENTECH's Xolair
(omalizumab, rhuMAb-E25)

A German researcher who did a retrospective study of the safety of Xolair concluded that the agent is very safe. However, he said it has not received European approval because European regulators are not convinced of its efficacy and are concerned about safety in children. If Xolair were approved in Europe, doctors said they will use for the 10%-20% of asthmatics who are most severe – provided there is reimbursement – but most were not convinced of its efficacy.

PFIZER and BOEHRINGER INGELHEIM's Spiriva
(tiotropium)

Spiriva has been approved in Europe, and the FDA issued an approvable letter. The drug got a very strong push at this meeting. Although Glaxo's Advair has become very popular in Europe as well as the U.S. and is being widely used off-label in COPD, every doctor questioned plans to use Spiriva, demonstrating once again Pfizer's marketing power. Interestingly, a speaker indicated that the marketing focus is likely to be on primary care doctors, not pulmonologists or COPD specialists. One expert said, "I believe Spiriva may be the first-line bronchodilator for patients requiring a maintenance dilator. This is the Procardia XL -- the once-a-day blood pressure medication – of COPD. This could become the QD bronchodilator. This, along with the TORCH study will change how we treat COPD." TORCH is a three-year, 5,000-patient trial sponsored by GlaxoSmithKline looking at survival in COPD with Advair. A Greek doctor said, "Spiriva is a winner." A GlaxoSmithKline official admitted, "Spiriva will be a big competitor for Advair."

Among the factors that should help Spiriva sales are:

- Advair use is off-label.
- Spiriva will be priced lower than Advair.
- Only 20%-30% of COPD patients are helped by an inhaled steroid.
- Spiriva also is good as add on therapy to Advair or salmeterol, though cost may make that prohibitive.
- QD dosing. A U.S. doctor said, "If it really is QD, that will be a big deal. It would allow us to simplify the treatment regimen. But the data is not impressive, and no shortness of breath label will be a big negative."

Asked about evidence favoring salmeterol over Spiriva at the FDA panel meeting, a speaker said, "I don't think we should be fighting salmeterol against tiotropium. I think comparing them is important for marketing but not for us as physicians. Doctors should have the ability to choose one or the other. If the TORCH trials shows mortality is changed by use of an inhaled steroid with a bronchodilator, then the playing field will change. Right now, we are discussing minutia. I think drugs are very good and utilize different methods of action, and they both should be in our armamentarium, instead of choosing or the other."

Pfizer may not be able to use the same marketing approach to marketing in the U.S. because the FDA has indicated that it will not allow a dyspnea indication. A BI official admitted the FDA position is disappointing, and Pfizer officials said they are still trying to change the FDA's mind and convince the agency to allow the dyspnea labeling. A Pfizer official said, "We've demonstrated an effect on dyspnea, and we will work with the FDA on getting that in the label." A source said the FDA didn't have confidence in the dyspnea data because of concern that a spirometer to measure of inspiration is more

reliable than the BDITDI (Baseline Dyspnea Index and Transitional Dyspnea Index) measure that was used in the trials."

SCHERING PLOUGH'S Asmanex
(dry powder mometasone)

Sales reps at the SGP booth were telling doctors that manufacturing problems are getting resolved and Asmanex will be available in Europe in the first quarter of 2003 and by mid-year in the U.S. Sources like the delivery device, but they predicted it would have trouble selling against a more-entrenched Advair. A U.K. doctor said, "the QD dosing makes it preferable, but the data and the cost will dictate what we use." A U.S. doctor agreed, "If Asmanex is QD, that will be an advantage. Fluticasone is a dry powder inhaled steroid, but it is in a sub-optimal delivery device, the Diskhaler."

New data in a pediatric population showed the drug is efficacious and safe at 100 mg and 200 mg QD and BID. A researcher said, "The systemic effects were negligible at 100 mg, and we just start to see them at 200 mg."

ANTIMICROBIALS/ANTIBIOTICS

Annually, there are 350,000-500,000 cases of community-acquired pneumonia (CAP) in Germany and more than 700,000 cases in France. CAP is the sixth leading case of death in the U.S. Two new antibiotics to treat CAP got a fair amount of attention at this meeting – Bayer's Avelox (moxifloxacin) and Aventis' Ketek (telithromycin). Most anti-infective trials are geared to equivalency not superiority, so, a speaker concluded, "Clinical trials may not hold the answer in how to choose an antimicrobial."

BAYER's Avelox
(moxifloxacin)

This is approved in for soft tissue infections in IV formulation in the U.S. and Germany and in an oral formulation in the U.S. and Europe for treatment of acute bacterial exacerbation of chronic bronchitis (ABECB), acute bacterial sinusitis (ABS), and community-acquired pneumonia (CAP). The 628-patient TARGET trial in Europe comparing IV moxifloxacin followed by oral moxifloxacin to IV/PO amoxicillin found the two regimens similar in terms of efficacy, but moxifloxacin 9%-12% less expensive than amoxicillin, mostly due to a shorter length of hospital stay. The 670-patient MOSAIC of moxifloxacin in AECB found five-day moxifloxacin treatment was associated with a significantly higher clinical resolution rate compared to seven-day standard therapy in AECB, but that moxifloxacin had a superior bacteriologic effect.

AVENTIS's Ketek
(telithromycin)

This first-in-class ketolide was recently submitted to the FDA, based on data on 1,000 patients. Researchers reported that a retrospective look at six telithromycin studies in high risk CAP patients found 800 mg telithromycin qd for 7-10 days is equivalent in efficacy and safety to amoxicillin and other comparator antibiotics. A speaker said, "Mortality with telithromycin is comparable to the comparators, and in our regulatory filings, it is holding up. When we look at individual cases, there doesn't appear to be any risk factors, but there have only been handful of deaths." It was also shown to be equivalent to comparators in AECB and effective in macrolide-resistant strains of strep pneumonia.

However, several experts questioned the results because the mean age of the patients in these trials was 44, which was described as "20 years below the CAP average age," suggests the results may not be applicable to elderly patients. In response to a charge by a competitor that it may not work well in flu, an Aventis researcher said, "The clinical cure outcome was identical for strep and pneumonia. In the bacteriologic outcome, telithromycin was better than the competitor in strep, but the comparator was a little better (~55) in flu."

PFIZER's Zithromax
(azithromycin)

A Pfizer official admitted that moxifloxacin and telithromycin are cutting into Zithromax sales, but they pointed out that Zithromax is easier to give and has a shorter duration of treatment.

Antibiotic Comparison

	Azithromycin	Moxifloxacin	Telithromycin
Dosing	QD x 3	QD x 5	QD x 7-10
Type of antibiotic	Macrolide	Fluoroquinolone	Ketolide
Disadvantage	Increasing pneumococcal resistance, variable activity in flu, GI side effects	Increasing pneumococcal resistance, absorption decreased by antacids, hepatoxicity, QTc prolongation, torsade des pointes, changes in blood glucose	May not work well in flu Potential liver and QTc issues
Advantage	Good activity against atypical and typical pathogens, can be used in penicillin allergic patients	Good activity against atypical and typical pathogens, can be used in penicillin-allergic patients	Works in macrolide-resistant strep pneumonia