TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

59th Meeting

This transcript has not been edited or corrected, but appears as received from the commerical transcribing service. Accordingly the Food and Drug Administration makes no representation as to its accuracy.

Pages 1 thru 226

Rockville, Maryland
June 19, 1998

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

59th MEETING

Friday, June 19, 1998

8:00 a.m.

Doubletree Hotel
Plaza I and II
Rockville, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

PARTICIPANTS

F. Blaine Hollinger, M.D., Chairperson
Linda Smallwood, Ph.D., Executive Secretary

MEMBERS

John V. Boyle, Ph.D.
Corey S. Dubin
Norig Ellison , M.D.
Richard J. Kagan, M.D.
Marion A. Koerper, M.D.
Jeanne V. Linden, M.D.
William J. Martone, M.D.
Mark A. Mitchell, M.D.
Kenrad E. Nelson, M.D.
David F. Stroncek, M.D.
Kwaku Ohene-Frempong, M.D.

TEMPORARY VOTING MEMBER

Paul R. McCurdy, M.D.
Lemuel Moye, M.D., Ph.D.
Ralph B. D'Agostino, Ph.D.

NON-VOTING REPRESENTATIVES

Katherine E. Knowles, Consumer Representative
Donald H. Buchholz, M.D., Industry Representative

GUESTS

Mary E. Chamberland, M.D.
James K. Stoller, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Opening Comments and Introductions

DR. SMALLWOOD: Good morning, and welcome to the second day's session of the 59th meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary of the Committee. Yesterday I read the conflict of interest statement. That statement still applies to today's proceedings, and if anyone desires to review that, it is available.

I would also like to ask that if there are any additional disclosures to be made regarding this meeting, that this be done at this time.

Just before we proceed, I would like to introduce additional members of the Committee that will be participating with us today with regard to the proceedings. We have Dr. Ohene-Frempong who is a member of the Blood Products Advisory Committee. Dr. Ohene-Frempong, would you please raise your hand? He is with us today.

We have temporary voting members that will be assisting the Committee today, Dr. Ralph D'Agostino and Dr. Lemuel Moye. We also have again Dr. Mary Chamberland, from CDC as a guest of the Committee, and Dr. James Stoller who is a guest of the Committee. We also have distinguished speakers from Europe who are listed on the agenda, and they will be making presentations this morning.

I would just like to bring to your attention that we have a very full agenda this morning. We will be adhering strictly to the time restrictions, and we would appreciate your indulgence in that.

At this time I will turn the proceedings over to our Chairman Dr. Hollinger. Thank you.

DR. HOLLINGER: Thank you, Dr. Smallwood. We do have a full agenda today, and on a very important topic, looking at clinical trial designs for alpha-1 proteinase inhibitor for the disease alpha-1 antitrypsin deficiency, which is an important disease in this country not only for its pulmonary for some liver disease also. So, we are going to begin then with an introduction and background to the problem or to the issues, and Dr. Ross Pierce, who is Acting Deputy Director for the Office of Blood Research and Review, will begin the session this morning. Dr. Pierce?

Review of Clinical Trial Design for Alpha-1 Proteinase Inhibitor

Introduction and Background

DR. PIERCE: Thank you.

[Slide]

So, this morning we will be talking about alpha-1 antitrypsin deficiency or alpha-1 anti-proteinase deficiency.

[Slide]

There may be a total of as many as perhaps 80,000 people in the United States who carry the severe form of deficiency for alpha-1 proteinase inhibitor and, yet, only about 4000 patients have been diagnosed. It is believed that the majority of deficient homozygotes will probably never develop emphysema in their lifetimes. Why is that?

Well, at least two things must occur in order to develop emphysema in this disease. Having the low level in the blood and the lung of this anti-elastase, this inhibitor of enzymes which break down lung tissue, and an enzyme which also is important in its anti-inflammatory properties in order for the normal balance of elastase, the destructive process, to be inhibited, the elastase/anti-elastase balance, there must be an appropriate ratio of neutrophil elastase in the lung and alpha-1 anti-proteinase inhibitor.

So, in addition to the decrease in alpha-1 proteinase, it is necessary to have repeated insults of increased neutrophil elastase which can occur through environmental factors such as smoking and neutrophil recruitment, or it can occur, in addition, through heritable factors which increase predisposition to recurrent bouts of lower respiratory tract infections.

[Slide]

Candidates for additional heritable factors that may be necessary to bring out the phenotype events of

emphysema in patients with severe and also moderate alpha-1 anti-antitrypsin deficiency include neutrophil burden, for which there is evidence; reactive airways disease, for which there is evidence also from the NHLBI registry study which we will hear more about today; elastase content of neutrophils has been proposed to vary; robustness of the inflammatory response; and variability in alpha-1 PI acute-phase response, which we will also talk more about later.

[Slide]

There is a large variety of genetic variants of the enzyme alpha-1 proteinase inhibitor. We can see that the risk for COPD, chronic obstructive pulmonary disease, approximately follows a gradient according to the levels of the enzyme in the blood and presumably in the lungs. The lung measurements have never been published for people with intermediate levels who are heterozygotes.

The designations refer to mobility on isoelectric focusing. The MM is the wild type, which is the normal situation where the serum level is between 20 and about 50 microM, and levels in the lung are about one-tenth that in the serum.

The homozygous, ZZ, patients have levels of only about 15-20% of normal and that corresponds to about an average of 6 microM. Even non-smoker ZZ patients may develop emphysema but most non-smoker ZZ patients probably

do not.

SZ patients are compound heterozygotes and show levels from 80 to up to 24 microM, up to about half of the normal values in the serum. It seems clear that smokers with SZ phenotype are at increased risk. In fact, a large study of nearly 60 SZ patients, comparing them to the NHLBI registry patients, the SZ patients were identified in that study by Turino and co-workers as the screening population for the NHLBI registry. There, if you were a smoker, a current smoker or an ex-smoker, the severity of your lung disease was comparable to that of the ZZ patients. So, SZ and ZZ were the same for the smokers in terms of lung disease, although the non-smokers, the ZZ patients, clearly were much more susceptible. The MZ patients have levels about 55% of normal, and some MZ phenotypes will also show emphysema.

[Slide]

In 1987, the FDA approved Bayer's Prolastin brand of alpha-1 PI for use by the intravenous route, and it was approved in terms of efficacy on the basis of the following unvalidated surrogate endpoints: Demonstration of maintenance of serum alpha-1 PI levels of greater than 11 microM; and an increment in epithelial lining fluid of alpha-1 PI from bronchopulmonary lavage.

There was a joint NIH-FDA meeting, back over ten

years ago, that had suggested that in treating this disease we should try to raise the level in the lung to that of heterozygotes. But, as I mentioned, there is a paucity of data on actual lung levels of alpha-1 PI in heterozygous patients.

[Slide]

So, where did the 11 microM target for therapy in this disease come from? Well, it turns out that it was actually fairly arbitrary. Gadek and Crystal wrote, in 1983, in Stanbury's text that it seems likely that there is a threshold level of alpha-1 antitrypsin for which the development of destructive lung disease is likely and above which it is not.

Now, the selection of 11 microM was not really data driven, except that at the time the phenotypes associated with destructive lung disease were felt to have levels of 35% or less than normal. That would include the null patients, ZZ phenotype, and the SZ phenotype and at the time their levels were thought to range up to 35%. But now it is known that their levels range up to about half of normal.

[Slide]

Here we see the distribution of levels of alpha-1 PI in the blood for the SZ compound heterozygotes. This is the theoretical threshold of 11, the theoretical protective

threshold, and you can see that about one-fifth of the patients have levels below this, and the levels have a mean or median here of about 15 and in other labs it is 17 microM, and the range goes all the way up to 24, which actually overlaps with the normal.

You might ask what is the distribution of lung disease within these individuals, and we will find that a significant number of individuals in this range have lung disease, and it is not just confined to those below the threshold of 11 microM.

[Slide]

In that study of nearly 60 subjects the cut point of 11 microM failed to differentiate the individuals who had COPD from those who were free of lung disease. The SZ individuals who had a level of over 11 microM who were fairly young -- they had a mean age of 49 -- had average FEV-1 or first expiratory volume in 1 second, a pulmonary function test measuring lung obstruction as a percent of normal -- their values were an average of 54%, distinctly abnormal. Under 80% is abnormal. And diffusion capacity, which is impaired in emphysema specifically, of an average of 63%. The levels ranged as low as 15-18%, extremely low levels that correlate with a very poor prognosis and usually death within 5 years.

So, Turino and workers just two years ago

concluded that in smokers the SZ phenotype confers a significant risk of chronic obstructive pulmonary disease, and they did have some examples of non-smokers with the SZ phenotype who also had developed emphysema.

[Slide]

The MZ heterozygotes, whose levels are a bit higher than those of the SZ on an average but where there is overlap, they too do not seem to be completely out of the woods with respect to risk of chronic obstructive pulmonary disease. This is a compilation of studies published in The New England Journal of Medicine by Morse in which patients who were attending a chest clinic and were identified as having COPD were then examined for the prevalence of the MZ heterozygous phenotype and compared to healthy controls.

There appears to be a fairly consistent enrichment among the lung disease patients, the COPD patients, for the MZ phenotype as compared to the controls, and I believe that a meta-analysis of these diverse studies from different geographical locations, accounting for variability in absolute percentages, would show and suggest significance. However, in population-based screening studies this has not been borne out, which may be related to the size of the screening population being inadequate to identify both symptomatic SZ and ZZ individuals and compare their relative risks for prevalence of COPD.

[Slide]

In this disease it is vitally important to understand the acute phase response. In response to lung infection normals can boost their levels of alpha-1 PI by 2- or 3-fold. In this slide, as a surrogate for lung infection individuals who are in the severely deficient range corresponding to homozygotes, in the intermediate range corresponding to heterozygotes, and in the normal range at baseline were challenged with typhoid vaccine. It can be seen that the homozygotes, severely deficient patients, barely bumped their alpha-1 PI levels in the blood. We can presume that the lung levels didn't go up either.

In contrast, the people who had intermediate, levels typical for SZ patients and some MZ patients, were able to raise their levels significantly, up to a level of about 25 microM, into the normal basal range. The rise in alpha-1 PI has been documented for normal subjects also with community-acquired pneumonia when such patients were brought back 6 months later and remeasured.

[Slide]

Thus, it is logical to believe that alpha-1 PI deficient patients may need to have their alpha-1 PI lung and serum levels maintained above levels to which MZ and ZZ heterozygotes are capable of boosting their levels during time of pulmonary infection or exacerbation of COPD. That

would point to a target serum level of about 25 microM, which would correspond to about 2.5 microM in the lungs. Those are levels significantly greater than what are typically achieved with 60 malignant IV per week.

[Slide]

In fact, in data with Bayer's Prolastin the mean trough steady state serum level of alpha-1 PI was about 17 microM, but this can range down to 11 or 12 microM. This shows data that Centeon was kind enough to share with us today. They did a dose-ranging trial in which patients, 3 in each group, were dosed at either 30, 60 or 120 malignant IV at a single dose, and those that received the same dose as is marketed for Prolastin produced lung levels that ranged from 0.5-1.4 microM, a mean of 1.28. Remember, we might hypothesize that a target level would be reasonable at 2.5.

Weavers found with Prolastin when he studied 9 subjects a mean epithelial lining fluid level for alpha-1 PI of 1.9, but from the standard error of the mean we can tell that some subjects probably had levels below 1, and the mean was about half of what is seen in normals.

The dose of 120, namely double the dose that is conventionally given in this disease and double the label dose, gave 7-day trough levels of 1.4 to 2.4 microM, after single dose, and this would correspond to predicted levels

of approximately 1.8 to 2.7, closer to the theoretical target that I had talked about of 2.5. I should mention that the levels are very dynamic when the product is given intravenously in contrast to the steady production by the liver in the normal situation. The supplementation produces temporarily levels that are above normal and then drop to these lower trough levels in the last days of the in-between treatment interval.

[Slide]

So, questions today for the Committee focus on what should be the appropriate endpoints to be studied to establish the efficacy of new IV alpha-1 PI products? And, should we continue to rely on the unvalidated surrogate endpoint cut point of 11 microM for a trough level?

What endpoints should be studied for the new aerosol products which are coming down the pike?

How should pivotal phase III studies be designed in terms of endpoints and in terms of control groups?

What should be the role and design of phase IV post-marketing studies? I should mention that presently FDA has no ability to force a company to do a post-marketing study except in the special case of where the product is granted accelerated approval. Thank you.

DR. HOLLINGER: Thank you, Dr. Pierce. We are now going to start with some of the pathophysiology. So, the

next one is going to be by Dr. Mark Brantly, from the NHBLI, on pathophysiology and alpha-1 proteinase mechanisms of action. Dr. Brantly?

Pathophysiology and Alpha-1 Proteinase Mechanisms of Action

DR. BRANTLY: Thank you very much.

[Slide]

What I would like to do is provide a little bit of background regarding lung biology, adding a little bit to what Dr. Pierce just said, and then I would like to go into some details about some studies that have been done recently at NIH regarding the biology of the lung in alpha-1 antitrypsin deficient individuals.

[Slide]

Just to start off with a summary and some basic information, it is a common genetic disease, alpha-1 antitrypsin deficiency. There are 75,000 to 100,000 individuals. The alpha-1 antitrypsin levels are about 5.75 microM, and the vast majority of individuals are PI Z, about 95%. This is in contrast to something like cystic fibrosis where there are multiple alleles that make up the phenotype. The vast majority of patients are a single gene defect that is PI Z. As far as their lung disease, they typically have emphysema and asthma and, indeed, the asthmatic component is up to 45%.

The average FEV-1 rate of decline is 83.5 ml/year

for the group that have FEV-1 between 35% and 80% of predicted, and it is about 3- to 4-fold normal. We all lose some lung function every year. It is about 20 ml or 30 ml. These individuals have accelerated loss of their lung function. The reactive airways or asthmatic component correlates with increased rate of decline, and we have had intravenous augmentation therapy for approximately 10 years now.

[Slide]

Now, alpha-1 antitrypsin is a plentiful serum protein. It is actually quite small. It gets into most tissues. It is an acute phase reactant. That is, it goes up with stimulation from infections and such and has anti-inflammatory properties. It is made predominantly in liver but it is made in many different cells within the body. It has a reactive site loop, which this area right here, that interacts with the neutrophil elastase, and it has oxidizable methionines which actually decrease the function of the molecule. It is very rich in methionines. It inhibits several types of proteases including the neutrophil elastase. In addition, it inhibits the cytotoxicity of neutrophil defensins, a pore-forming molecule which I will talk about in a little more detail.

There is some suggestion in recent data that alpha-1 antitrypsin actually may act as a scavenger for

oxidants but I don't think that has been confirmed really.

[Slide]

This is a CT scan of an alpha-1 antitrypsin deficient individual. Basically, this was an individual that previously had no evidence of lung destruction and then, following pneumonia, was scanned and developed basically these large bullae. Radiographic features include emphysema bronchiectasis and oftentimes bullae formation. Clearly, high resolution CT is one of the most sensitive ways to detect lung destruction in these individuals even long before individuals have developed pulmonary function abnormalities.

[Slide]

Again, I want to keep driving home this is one of the clinical parameters we use. These individuals basically lose lung function much faster. This is the FEV-1, or the delta FEV-1, or also what we call the rate of decline. You can see that there are individuals that are losing up to 250 ml per year. Again, I will remind you that 20 ml or 30 ml is the normal rate. So there are individuals in here that are going much, much faster. In addition, they also lose DLCO, which is an indirect measurement of the number of functioning air sacs an individual has.

[Slide]

Most importantly, the consequences of this rapid

rate of lung function decline is that people die earlier. This is a Kaplan-Meier survival analysis from Dr. Crystal's laboratory from approximately 10 years ago where he looked at the survival of a group of people referred to NIH compared to the normal population.

The point is that only 52% of the alpha-1 antitrypsin deficient individuals that had pulmonary symptoms are alive at age 50, and only 16% of them are alive at age 62. The most common causes of death were emphysema, infection, sepsis and liver disease.

[Slide]

Now let's talk a little bit about the biology in a little bit more detail. This is sort of a cartoon of a normal acinus. That is, typically there are very few neutrophils, which this is a representation of, and very little neutrophil elastase, and there is lots of alpha-1 antitrypsin. In the alpha-1 antitrypsin deficient acinus there is a lot of neutrophils and there is a lot of neutrophil elastase, and there is very little in the way of alpha-1 antitrypsin to basically block that. It is the absence of sufficient alpha-1 antitrypsin in the lower respiratory tract which is associated with the destruction of the alveoli by neutrophil elastase and probably other neutrophil-derived factors.

[Slide]

It is clear that the lung destruction is the result of loss of the functioning gas exchange units, and that at least in part the lung destruction is the result of proteolytic damage. The proteolytic damage appears to be predominantly from the neutrophils but there is some suggestion that the alveolar macrophages may play a role also. That can be seen particularly from work from Dr. Shapiro, from Washington University. There are increases in neutrophils in response to infection, smoking and perhaps even environment pollutants. These is an emphysematous acini and these are normal acini.

[Slide]

This concept sort of engenders this protease/anti-protease balance concept within the lung. In a normal individual there is very little in the way of neutrophil elastase or toxic neutrophil products and there is an overwhelming amount of anti-neutrophil elastase protection in the lung. In alpha-1 antitrypsin deficient individuals that have developed lung disease there is a burden of neutrophil elastase and there is very little in the way of neutrophil elastase protection. Therefore, the lung damage is the result of basically two phenomena occurring. That is, there is a burden of neutrophils that are activating releasing products and there is a lack of sufficient alpha-1 antitrypsin.

[Slide]

One way to sort of look at the formation of lung disease in alpha-1 antitrypsin deficient individuals is to look at it basically in stages. This is a little bit artificial but it helps us sort of think about the biology a little bit. There is the initiation phase; there is a maintenance phase; and there are sort of effectors of injury.

The initiators we know well are cigarette smoking and infections. But what happens then? Well, basically there is a dynamic relationship between pro-inflammatory cells like the neutrophils and the alveolar macrophages that sit within the lung, and also pro-inflammatory molecules which basically cause recruitment of neutrophils that cause an expansion in the cell number, and then activation of neutrophils. That is, they are capable of releasing the toxic substances that normally would be used to kill bacterial infections and then released.

The substances that we know probably are effectors of injury include oxidants, proteases and most recently we know now that neutrophil defensins also play a major role. Indeed, there are clearly some feedback mechanisms in which defensins probably drive alveolar macrophages to make pro-inflammatory molecules also.

The point that I would like to make here is that

this is the stage of destruction. This is the stage of inflammation. Typically, inflammation precedes destruction or they are concomitant.

[Slide]

For neutrophils the major pool is the blood. They are only present in the lung in only very low numbers, about 1%. They have several toxic products, including oxidants, neutrophil elastase, cathepsin G, protease 3 and defensins. But they are attracted to the lung over 1% in response to inflammatory factors such as LTB4, IL-8 and other chemotractant factors which basically drive a gradient which attracts the neutrophils to say, "come on, boys, we're having a dinner here."

[Slide]

Now, neutrophil elastase is a small glycoprotein. It has a triad that interacts with the reactor site loop of the alpha-1 antitrypsin and it cleaves it such that the neutrophil elastase and alpha-1 antitrypsin are joined together in a covalent way that basically takes out the neutrophil elastase completely.

It is synthesized in the myeloid precursor cells and it is stored in these azurophilic granules which are ready to basically be released, and it degrades mostly to soluble protein components, including cell surface receptors which are important in defense of infections. One of its

major functions appears to be inhibited by alpha-1 antitrypsin.

[Slide]

Neutrophil defensins are another molecule within the azurophilic granule that also are quite, quite toxic. A lot of attention recently has been turning towards this as an important molecule in causing lung damage. It is quite a small molecule. It forms pores. It actually punches holes in cells. It punches holes in cells of bacteria, viruses and also in human cells. It has a wide spectrum of cytotoxicity and kills many different types of cells. It belongs to an alpha defensin family. It makes up about 30% of the azurophilic granule. In other words, there is a lot of it in the cells. Interestingly enough, the cytotoxicity of neutrophil defensins is inhibited by alpha-1 antitrypsin.

[Slide]

We are interested in knowing what the interplay is between these biological substances in alpha-1 antitrypsin. So, at NIH one of the things we did was we recruited a group of alpha-1 antitrypsin deficient individuals that had very mild lung disease, and wanted to compare them to a group of normal individuals and ask some questions about what is going on in the lungs very early on in the disease.

This is the study population. We had 22 alpha-1 antitrypsin-deficient individuals and 14 normal individuals.

This is the percent predicted of the average number of alpha-1-deficient individuals, and it is about 100% and it is slightly different from normal individuals but you can see there is a span. None of them dropped below 70% of the predicted. So, again, we are looking at a mild lesion in these individuals.

[Slide]

Let me tell you a little bit about what is going on in their lung. Number one, they were characterized in their serum by having about 5-fold less alpha-1 antitrypsin in their blood as compared to normal individuals.

[Slide]

This was reflected in addition with about a 10-fold difference in the amount in their lung. So, again, there is about 10 times less alpha-1 antitrypsin in their lungs protecting them.

[Slide]

In addition, even in these individuals that had very, very mild lung disease there was a burden of neutrophils. You can see there is quite a spread of it. These individuals had on the average about 3 to 3.5 times more neutrophils in their lungs than norma. That is important to remember, that it is compared to normal individuals who had about 1%.

[Slide]

If you looked at some of the biological substances what you found was that there were increased amounts of neutrophil defensins and, indeed, there was about 42 times more neutrophil defensins in the lungs of even these patients that had mild lung disease than normal individuals.

[Slide]

There was about 33 times more neutrophil elastase in the lung as compared to normal individuals. You can see that there are some individuals that are down towards low. This actually sort of sits on the bottom, right here, and I will give you some numbers in just a moment. But, again, the picture I am trying to generate is that there are a lot of toxic neutrophil products even in the lungs of normal individuals.

[Slide]

One of the things that clearly alpha-1 antitrypsin is designed to do is inactivate neutrophil elastase, and one of the things that we assay for is the formation of complexes in alpha-1 antitrypsin-deficient individuals. But interestingly enough, when you look at the complexes in alpha-1 antitrypsin-deficient individuals it is really similar to the number of complexes in normal individuals. But in deficient individuals the complexes are limited by the amount of alpha-1 antitrypsin in the lung. In normal individuals the complexes are limited by the amount of

neutrophil elastase available in the lung.

[Slide]

The other thing that is important though is to ask the question what is the status of inflammation in the lung. Is there any inflammation in the lung? When you look at the presence of some of the biological factors that we know are a very potent stimulus for recruitment of neutrophils into the lung, what we find is a substance called LTB4 which is exceptionally powerful for attracting neutrophils. It is about 6.5 times higher in alpha-1 antitrypsin-deficient individuals as compared to normal individuals. So even in these patients who have mild lung disease, there are chemotractants that bring neutrophils into the lung.

[Slide]

In addition, there are other chemotractants, like IL-8 which also are increased in the lavage of these individuals at about 2.5 times the amount compared to normal individuals, but again there is quite a spread but on the average, again, there is an increase. Let me remind you one more time, these individuals have very, very mild lung dysfunction.

[Slide]

IL-6 is also elevated, which is another chemotractant and acute cytokine. You can see, about 2.5 times.

[Slide]

Finally, the early response pro-inflammatory molecule, IL-1-beta, is also increased by about 2.5 times as compared to normal. So, several of these cytokines that are associated with inflammation are elevated even in the mildest of lesions.

[Slide]

This is sort of a summary that all the cells in the lung in these individuals -- there is no difference between the alveolar macrophages and the lymphocytes between normal and alpha-1 antitrypsin-deficient individuals. The only difference is the neutrophils and there is clearly statistically a large amount of neutrophils as compared to normal individuals.

[Slide]

As far as the biological factors that are associated, you can see that there is a large amount of neutrophil elastase in the lungs of these individuals, statistically a huge difference. There is a difference in alpha-1 antitrypsin. The complexes are the same, as I mentioned, and the cytokines or pro-inflammatory substances are substantially increased, including LTB4. So there is ongoing inflammation in the lungs of these patients. That is the point.

[Slide]

Now, let's ask the question is there a relationship between some of these factors that are produced by the neutrophils and some of the inflammatory factors. This is what is called a correlation matrix. This is NE, and basically we are asking the question does neutrophil elastase have a relationship with any of the biological substances in a statistical manner?

Let me point out the ones it has a relationship with. If you look at the neutrophil elastase level and compare it to the IL-8 level you can see that there is a strong correlation between increasing amounts of neutrophil elastase and IL-8, increasing amounts of neutrophil elastase and neutrophil defensins, increasing neutrophil elastase and the neutrophil burden but, most importantly, increasing amounts of neutrophil elastase are associated with lower FEV-1s, increase in rate of decline of lung function and also lower DLCO.

The same thing also appears true of the other neutrophil toxic product, human neutrophil defensins. There is a strong correlation between the pro-inflammatory molecule IL-8 and the burden in neutrophils as well as lung dysfunction. That is, the higher the HNP, the lower the FEV-1, the lower the DLCO and the greater the decline the lung function is. So, there is significant correlation between many of these biological factors and inflammation

and rate of decline in lung function over time.

[Slide]

This sets the stage, but let's ask two different questions. One is, why is this happening? Number two, is there any possibility that alpha-1 antitrypsin may turn off the inflammatory response?

The answer is the following: This is an experiment where we took alveolar macrophages from bronchoalveolar lavage to be harvested from alpha-1 antitrypsin-deficient individuals and normal individuals. We used the molecule human neutrophil defensin, and we took the average amount that we found in the patients' lungs and stimulated the alveolar macrophages to see if they could make the chemotractant LTB4.

This is a control where basically there was no neutrophil defensin placed on the culture with the alveolar macrophages. When you add human neutrophil defensins, it increases the amount of LTB4. When you add neutrophil elastase, it increases a little bit. Interestingly, when you add both of them together it gives a huge amount of these chemotractant that is pulling in the neutrophils. But the interesting part is when you add alpha-1 antitrypsin in the typical amounts that we see in the lung, around 2 to 2.5 microM, what you get basically is a complete shut down of the amount of LTB4 and it is back down to baseline. I think

it is also the same with just HNP, just with alpha-1 antitrypsin. Normals have a similar response actually, but it is not nearly as exaggerated as it is, obviously, for alpha-1 antitrypsin-deficient individuals.

[Slide]

So in conclusion, lung destruction in alpha-1 antitrypsin-deficient individuals is mediated at least in part by the toxic products in neutrophils. There is a large amount of toxic products in the lungs of alpha-1 antitrypsin-deficient individuals and even at an early stage in their development of lung disease.

There are many inflammatory factors that can be detected. We have only looked at LTB4, IL-8, IL-1-beta and IL-6 and they definitely increase. The burden of neutrophil elastase and defensins correlates with increasing concentrations of pro-inflammatory factors in the lung. The burden of neutrophil elastase and defensins correlates with increasing lung function impairment and decline. Clearly, at least for some biological factors, alpha-1 antitrypsin can turn off the stimulus that bring in these chemotractants. Thank you.

DR. HOLLINGER: Thank you, Dr. Brantly. The next speaker is Ronald Crystal, from the NHBLI registry and he will provide information on clinical data. Dr. Crystal is from the New York Hospital, Cornell Medical Center.

NHLBI Registry Clinical Data

DR. CRYSTAL: Thank you. First a bit of background. The registry, as Committee members may have guessed from the presentations, almost everything you have heard in terms of the approval and so on was based on the work at the laboratory at the Heart, Lung and Blood Institute in the period of the '80s. After the approval, which was in '87 I think, I decided that the problem was done and I moved on to gene therapy which is my major interest now.

But when the Agency asked Bayer to carry out a phase IV, I suggested to Claude L'Enfant, the Director of the Institute, that perhaps the Institute should be involved. That was perhaps a mistake on my part because Claude then asked me to be the chairman. So, what I will do is wear my chairman hat of the registry and I will give you an overview and then a couple of thoughts about the problem that we are dealing with today.

[Slide]

The registry's objective was to characterize the clinical and laboratory course of alpha-1 antitrypsin deficiency whether or not the individuals were receiving augmentation therapy with intravenous alpha-1 antitrypsin.

The primary outcomes were mortality and decline of FEV-1 in relation of clinical characteristics in the use of

augmentation therapy. There were 37 centers, 1129 individuals greater than 18 years. Serum alpha-1 antitrypsin levels, 11 microM or ZZ genotype, and they have been followed for periods of 7 years.

[Slide]

A very important concept -- and I will come back to this in the summary -- is in terms of the design, and very important that the registry because of its inherent design is not -- I repeat not a clinical trial to evaluate the efficacy of alpha-1 antitrypsin augmentation therapy but is, rather, a mechanism to collect and analyze clinical data useful for understanding the natural history of the deficiency and primary outcomes already mentioned.

[Slide]

First the mortality data, and I have picked selective aspects that would be relevant to your discussions. The cumulative mortality in terms of months in the registry as it goes on, as you can see, is pretty constant, and a period of 5 years and there is 18.6% mortality. So, it is not a trivial problem to have.

[Slide]

This is probably the critical slide in the presentation. I must say, having carried out the studies and understanding that the registry is a registry and not a controlled trial, when I saw this data I was stunned. That

is, that there is decreased mortality. I didn't think that the registry would have the power, and with all the caveats with it, to show this. So, this is the cumulative mortality. This is months in the registry. These are individuals.

The blue line is never treated and the yellow line is always treated with alpha-1 antitrypsin. Very importantly, partially treated, and the partially treated and the never treated are similar. Partially treated was defined by the registry as not being on alpha-1 antitrypsin augmentation therapy for the first 3 months or for greater than 1 month during the course of their follow-ups. So, it could be anywhere from 1 month to missing 1 month or not being on it for 1 month of the whole period. So it is a mixed bag of individuals, but it is striking that this line is very similar.

In the analysis, the committee was concerned that perhaps these parameters may be in part due to what happened in the first 6 months. So in the analysis the first 6 months was eliminated. So, these are subjects with greater than 6 months follow-up. As you can see, it is still significant of those never on compared to always on therapy or partially on. Again, note that these two arms are very similar. That is a very, very relevant piece of information that I think is important in terms of consideration of what

the level should be. That is, if you are not on alpha-1 antitrypsin for some periods, and again it is variable and we don't have the data of how much they weren't on, but if you were on it you still have the survival advantage in terms of the therapy.

[Slide]

So, the conclusions for survival analysis were the overall mortality of 3 years, 11%; 5 years, 19%. Overall the recipients of augmentation therapy demonstrated a trend. The paper is being published I think this month or next month. But this is a summary of the paper. The recipients of augmentation therapy demonstrated a trend toward a lower mortality rate compared to those who did not receive augmentation therapy. Little can be said about the partial effects of augmentation therapy on survival among the subgroup of individuals with an FEV-1 greater than 50% because of the small numbers of deaths observed in that group.

[Slide]

In terms of the FEV-1, keeping in mind that FEV-1 is a surrogate marker, and we had a lot of discussion on the committee over many, many months of what are the categories, finally we decided that we should not impose it ourselves but we should take other groups' categorization. So, this if the American Thoracic Society categories of FEV-1. So

there are various stages. It was based on alpha-1 antitrypsin deficiency or COPD, but the important things were the less than 35%, 35-49%, 50-79% and then greater than 80%. We also did some pooled analyses. In other words, we took a standard classification and posed that on the registry.

[Slide]

The data showed in terms of FEV-1 a slope in milliliters per year, that only the group in the 35-49%, comparing on therapy versus not on, was significant. The other groups, less than 35% and 50-79% and greater than 80% were not.

[Slide]

Another way to look at the same data is plotting it in a continuous form. This is the FEV-1 slope in milliliters per year, and this is the mean FEV-1 as percent predicted. As you can see, the yellow line are those not on therapy and it goes down and then goes up. So, it is this group that accelerate the fastest, and the significance was in this group in this range, here.

[Slide]

The summary of the committee and as the paper summarizes is that the overall rate of FEV-1 decline is shown here. There was a more rapid rate of decline among males, current smokers, those ever with a bronchodilator

response, ages 30-44, those with FEV-1 between 35-49%, and those with serum alpha-1 level of less than 5.7 microM -- that is an important concept also, the lower your level the worse you do. Recipients of augmentation therapy demonstrated a trend towards lower rates of FEV-1 decline in the subgroup of FEV-1 35-49% predicted.

[Slide]

So the overall conclusions of the registry were that the observed trends for differences in mortality and FEV-1 decline are consistent with possible beneficial effects of augmentation therapy. Very importantly, these results must be interpreted cautiously. Since the registry is not a clinical trial, it is possible that these results are due to unknown differences between those who received and those who did not receive augmentation therapy.

My own view is very similar to this, but I think one caution that I would give the Committee in terms of evaluating the various comments today is that we can't have it both ways. If we accept the FEV-1 data and say, gee, there is a real problem other than in this one group, then we can't throw out the mortality data. So, I think we have to be cautious about all of this because it is a registry.

[Slide]

Just a couple of other comments because you have specific questions relating to it. Since we developed

epithelial lining for evaluation of the lavage concept I thought you might be interested in my view of it, I think it is useful in a qualitative sense but I think there is tremendous variability in the numbers. So, I would urge caution in putting too much emphasis on it. It is a very complex mixture and a variety of methodologies and, although being the inventor of it, I think we have to be very cautious about it overall.

[Slide]

Just a comment about the SZ because I have a somewhat different point of view than we have heard. This is the same data that you have seen in terms of serum alpha-1 antitrypsin level in microMolar amounts versus the phenotype being at risk for emphysema. This is the concept that you heard articulated.

One thing that is important for you to keep in mind is what is the genotype of the population, and S is more common than Z. That is, there must be more SZs than there ZZs out there. Those 49 patients that you saw, that was presented before, as a co-author of that paper I can tell you that is seeing just the tip of the iceberg in terms of the total amount of SZs there. So, although there is no question that SZs are at risk. It is a very, very small percentage of individuals because the phenotype frequency is higher. From the WHO summary of the data a few years ago

was that it was 0.021, something like that, 0.22 for S compared to 0.014, I think, for Z. So, if there is an issue in terms of the number of ZZs and where are most of the ZZs, it is much more for the SZs because very few in percentage of the genotype frequency have bee found.

[Slide]

Also keep in mind when you are thinking about the levels that this is from the pivotal trial and it is just one of the figures that was in The New England Journal paper, but this is for 5 individuals, just as an example, and keep in mind here is that threshold level, and keep in mind that when you integrate it under the area of the curve, in a huge amount of time these individuals have levels that are much higher than that trial level.

[Slide]

Finally, coming back to this mortality data again, it is important to keep in mind that the partially treated versus the always treated -- no difference. All that together, at least my view of it or my conclusion from that is that the levels of 11 microM are probably very, very reasonable, and in terms of cost effectiveness of increasing those levels, probably it is not going to make a significant difference.

[Slide]

Finally, let me just give you my own personal

summary. This is not the registry. This is the view that Jim Gadek and I had when we started this and we got the idea of doing all this. And, I haven't changed -- Walter Reuther's comment about if it looks like a duck, walks like a duck and quacks like a duck, then it just might be a duck.

[Slide]

Jim Gadek and I, back in '78 or so when we thought about all this was -- if there is a systemic deficiency of alpha-1 antitrypsin, then augmentation of the levels would protect the lung. My overview, and keep in mind that I am not working in the field other than chairing the registry, is that there is no information that changes my view in terms of the levels of alpha-1 antitrypsin that should be achieved. Thank you.

DR. HOLLINGER: Thank you. The next discussant is Mark Schluchter, who also will be looking at the statistical data from the NHLBI registry. Dr. Schluchter is from Case Western Reserve University.

NHLBI Registry Statistical Data

DR. SCHLUCHTER: Good morning.

[Slide]

The purpose of my talk this morning is to present estimates of sample size for a clinical trial of augmentation therapy where we estimate the parameters, such as variability estimates and mortality rates, using the

recently completed NHLBI registry data to see what the implications are in terms of required sample size for a clinical trial.

I will also compare these estimates to some previous estimates that were reported by Idell and Cohen, back in 1983. They used data retrospectively collected as part of the workshop on IZ emphysema that was set up by the NHLBI in 1980.

I will look at two cases today. The first will be the case where the FEV-1 slope or FEV-1 decline is the outcome. Then I will look at mortality as an outcome.

[Slide]

So looking at the case where decline in FEV-1 is our outcome, some of the assumptions -- I will be assuming that we will be doing a 0.05 level test, a one-sided test, specifying the power of 0.9. That is, we will be designing a study to have 90% chance of finding a true difference of a certain size if, in fact, that difference exists.

Assuming that the eligibility criteria are fairly similar to what was in the NHLBI registry subjects 18 years or older, also implicitly those without some alpha-1 level less than or equal to 11 microM were at high risk phenotype. I will look at several scenarios in terms of design. For lengths of follow-up I will look at studies of 3, 4 and 5 years, and I will look at the case where we have 2

measurements of FEV-1 per year per subject and the case where we have FEV-1 more often, or 4 measurements per year.

[Slide]

A major consideration in designing a clinical trial is in terms of what range of FEV-1 percent predicted baseline to use as an inclusion criteria. From the results that Dr. Crystal just presented, we saw that in our registry in the primary results paper we found that the effect of augmentation therapy, the apparent effect, did appear to differ quite drastically according to the level of FEV-1 decline. In that paper, for reasons of worrying about such things as regression of the mean, we stratified patients according to their mean FEV-1 percent predicted across follow-up.

On the other hand, in designing a study you wouldn't know the mean FEV-1. It is more relevant to stratify patients by their baseline FEV-1 percent predicted. Therefore, in this talk I am going to present results both ways, where I have stratified patients both by their mean FEV-1 for consistency with the paper, as well as by baseline FEV-1. I will be looking at 4 different FEV-1 subgroups which parallel the groups that we reported in the paper, the 35-49% predicted group or stage 2 COPD; stage 1 COPD, 50-69% predicted; the pooled group, 35-79%; and then a group 30-65% predicted which is the range of FEV-1 considered in the

earlier calculations by Idell and Cohen.

[Slide]

Just briefly, the statistical model we assume is what is known as a linear random effects model. We assume that each subject's measurements of FEV-1 follow a linear regression over time with a random intercept in slope and where the mean slope can depend on the patient characteristics such as age, sex and so on.

So for simplicity, I will assume that we have N subjects measured at the same set of visit times or years, t1 up to tK. The mean slope for that group is going to have a variance, sigma squared over N, where the variance, sigma squared, is a function of a between-subjects variance, sigma squared B, and a within-subjects variance, sigma squared E. We will be estimating these from the registry data to use those in sample size calculations.

[Slide]

The sample size formula then -- the other thing we have to specify is the size of the difference in mean slopes between those receiving or not receiving therapy that we would like to detect, and I will call that delta. The sample size per group then is given by this formula which involves, again, sigma squared involving our 2 variance components and the size of the difference that we want to detect, as well as some terms that involve the type 1 and

type 2 errors.

[Slide]

So, again, the things that we need to estimate from the registry are the variance components and the mean FEV-1 slopes for those not on and on therapy or, more importantly, the difference in slopes, delta, and we might want to look at that as the percent reduction in slope, the difference in slopes divided by the mean slope in those not receiving therapy.

[Slide]

This slide shows the estimates of the variance components, sigma B and sigma E that we obtained from our registry data. Again, the rows are the 4 groups we are interested in. The first 2 columns are patients grouped by the baseline FEV-1, giving their between component and within component. The second set of columns are patients grouped by mean FEV-1. These would be used in the sample size calculations. It is not important to dwell on them but we note that the between-subjects standard deviations range in this table from 50 up to 60 regardless of method or group, and the within-subjects standard deviations range from 111 to 125 regardless of which method we are using or which stratum.

[Slide]

This table shows the estimates of the effect of

augmentation therapy in terms of the difference in slopes, receiving versus not receiving therapy. Again, on the left are patients stratified by baseline FEV-1, on the right by their mean FEV-1 for our 4 strata. So, for example in the 35-49% group stratifying patients by baseline FEV-1 the estimated slope was 81 ml/year in untreated, and the difference in slopes was 23 ml/year, which represented a 28% reduction in slope due to augmentation.

If we look at patients grouped by mean FEV-1, the slope was slightly more negative in the untreated, 93 ml/year and the difference was 27. If we look at the other different groups we can see the differences in slopes, 50-70% was 14 or 8; at 35-79% the difference in slope is 15 ml/year, 14 ml/year; and in the 30-65% group, 21 ml/year difference or 18 ml/year.

[Slide]

Now I will present 4 different tables corresponding to these 4 groups showing what sample size would be needed to detect this size of a difference, using estimates of variability from the registry.

So this slide looks at the group of 35-49% predicted. Again, the first 2 columns are stratifying by baseline FEV-1, the second 2 by mean FEV-1. We then look at the cases where we have 2 measurements per year or 4 measurements per year within each method, and then 3

different durations of follow-up, 3, 4 and 5 years.

So, for example, with a 3-year study and patients stratified by baseline FEV-1 we would need 150 patients per group to detect a 23 ml/year difference. And, very similar results if patients are stratified by mean FEV-1, 151 patients per group. As we increase the length of follow-up the number of patients required is reduced down to around 100 with both methods. If we take measurements more often we get some reduction although not a great reduction in the sample size.

[Slide]

This slide is a similar table looking at the 50-79% predicted group. Here the differences were less, 14 ml/year stratified by baseline and only 8 ml/year stratified by mean. Because these differences are less, you would need a much larger sample size to detect those. You can see samples sizes of 800 to 1200 here stratified by mean FEV-1, and sample sizes, say, from 340 to 350 for a 5-year study; 430 to 500 for a 3-year study.

[Slide]

If we look at the combined group, 35-79% predicted, again the observed differences were around 15 ml/year or 14 ml/year. I will just focus on stratifying by baseline FEV-1 here. For a 5-year study, roughly between 270 to 290 patients per group, and for a 3-year study

between 340 to 400 patients per group.

[Slide]

The last slide is the pooled group, 30-65%. Here we observe somewhat greater deltas and we would need sample sizes for a 5-year study around 110-114 per group, and for a 3-year study 140-170 per group.

[Slide]

This slide just compares the estimates from the current registry with the previous calculations. For example, looking at the estimate of the between-person standard deviation, using the retrospective data it was 114 ml/year. In the current registry it is more than half that. This is probably because the NHLBI registry data were prospectively collected with quality assurance versus retrospectively collected data.

Similarly, the within-person standard deviation is somewhat less with the NHLBI registry data. The estimates of the mean FEV-1 decline -- I should say this is in the 30-65% predicted group. The estimates are similar between the 2 analyses for the mean FEV-1 decline in the untreated but, because of the variability it is much less based on the current estimates. The required N per group to detect a 20 ml difference in slopes in a 4-year study was 569 earlier and now is 131, considerably less.

[Slide]

Moving on to looking at mortality as an outcome, again we will look at a one-sided test, 0.05 level alpha; power of 90%. We will consider a 5-year study where patients are enrolled over the first 2 years and then followed for an additional 3 years. We will look at 2 subgroups according to baseline FEV-1, the 35-59% predicted group which is the subgroup using the standard ATS subgroups. This is the group that showed the biggest apparent effect of augmentation on mortality. We will also look at the 20-65% group because that group was looked at in earlier calculations.

[Slide]

Estimates from the registry we need for sample size calculations for the 2 groups, the yearly mortality ranged between 8% and 9% depending on which subgroup we are looking at. Effect of augmentation therapy in terms of a risk ratio comparing those receiving versus those not receiving augmentation therapy, was 0.21 in the 35-49% group and 0.56 in the 20-65% group. These correspond to a 79% or 44% reduction in mortality, again particularly on the right with confidence intervals that don't include 1 and are somewhat wide.

[Slide]

Looking at the group 35-40% predicted, this slide shows the required sample size per treatment group to detect

different reductions in mortality. We would need 518 per group to detect a 30% reduction, 273 to detect 40%, 166 to detect a 50% reduction and, again, we observed based on our risk ratio a 79% reduction that would require 59 subjects per group.

[Slide]

In the broader range, 20-65% predicted, we would estimate we would need 553 patients per group for a 30% reduction; 292 to detect 40%; 177 for 50%; and 239 subjects per group to detect the observed 44% reduction that we estimated from the data.

[Slide]

This slide just compares estimates of sample size using the current registry with the previous calculations for the 20-65% predicted group and generally the estimates are very close. For example, to detect a 30% reduction, earlier it was estimated 584 for group; we estimate 553 per group.

[Slide]

So just in conclusion then, in looking at FEV-1 decline as an outcome, we saw between-subject variability in FEV-1 rate of decline is much less than was previously estimated. Our sample size estimates do vary quite a bit depending on the entry criteria for baseline FEV-1 percent predicted. For example, we would estimate 284 per group

needed in the range of 35-79% predicted if the delta is 15 ml/year versus, for example, 114 per group in the range 30-65% predicted if the delta is 21 ml/year.

[Slide]

The mortality outcome, again in the subgroup 20-65% predicted we estimate 292 subjects per group would be needed to detect a 40% reduction in mortality. This was similar to the previous estimates in 1983. We would estimate needing 59 subjects per group in the 35-49% predicted group, and this should actually be 239 per group in the 20-65% predicted group.

If we factor in the variability in the estimates in the reduction of mortality, however, these sample sizes can become larger. Using the upper limit for the confidence interval in the first case, instead of 59 we would need 166 per group in the 35-49% predicted group. In the second case, the upper limit for the confidence interval where the reduction in mortality is very close to zero we would estimate needing a huge sample size if there was a very small reduction in mortality. Thank you.

DR. HOLLINGER: Thank you. The next speaker is Dr. Dirksen, from Copenhagen University Hospital, in Copenhagen, and he is going to talk on the randomized controlled clinical trial design issues. It will be very important for the Committee.

Randomized Controlled Clinical Trial Design Issues

DR. DIRKSEN: Thank you for inviting me. I shall report our experience from a randomized controlled clinical trial of augmentation therapy in patients with alpha-1 antitrypsin deficiency.

First, I will just tell you about the background of this study. As you know, the drug was registered in this country in 1988, and during the next year patients came to us in Denmark. They had read about this therapy and wanted to get the treatment. In Denmark we have a long tradition for registering people with this deficiency. So, we had a registry of several hundred people. Therefore, it was difficult for us just to start this treatment. It would be very expensive.

In '90, the government decided that people could only get this treatment if they participated in a randomized, placebo-controlled trial. That was, in fact, the start of this trial. In the first 2 years a big problem was local authorities because it was very difficult for them to accept to pay for the treatment which we, at that time, bought from Bayer.

After 2 years, the Danish Blood Transfusion Service, in collaboration with the French Blood Transfusion Service, were able to offer the drug for free in a trial. That changed the situation because for the first 2 years we

were only able to include 10 subjects, but then we could more than double the participants. Even more important, our Dutch colleagues were able to joint the study. In that way, we were able to enroll 26 patients from Denmark and 30 patients from Holland. That was in '93.

Then 2 years later, as a consequence of the HIV scandal, the French government decided to require documentation of all blood products that were registered in France. That forced the French Blood Transfusion Service to consider all their products, and at that time alpha-1 antitrypsin was probably the smallest product, or at least a very small one. So, they made the decision that they would not go on with the production of alpha-1 antitrypsin and that stopped our trial. At that time, they had some material left and it was decided that should be offered to participants so that everybody could be in the trial for at least 3 years.

[Slide]

The patient characteristics -- here you can see that the proportion of males and females was the same in Denmark, was equal, and in Holland there were twice as many males as women. You have the mean age, and here you have the lung function. Only patients with lung function below 70% predicted and above 35% predicted were included in the study. You can see from this that the participants in

Denmark and Holland were quite comparable.

The only measurement that was different was total lung capacity and residual volume, which was much more normal in the Danish group than in the Dutch group. The reason for that is simply a measurement technique because we used body box measurements and in Holland they used the helium dilution. So, I think this is not a real difference. The participants were allocated to active and placebo treatment equally in the two countries.

[Slide]

Here are the results of this study. This slide is a little bit too busy. Here, on the left, you have all the lung function measurements and 2 radiological measurements down here. First, I should say that the whole concept of this study was that from a theoretical point of view it should be possible to see an effect on far less subjects than had previously been anticipated because previous calculations were based on 6 monthly or yearly measurements, and from a theoretical point of view, by doing lung function measurements much more frequently it should be possible to see an effect in a shorter time with fewer people.

We, in fact, did the measurements twice daily, every morning and evening, and that is what is indicated by this PASS. PASS means patient administered serial spirometry. The result of that was very frustrating because

we found a correlation between these frequent measurements, and I won't go into detail on that. It will come out in the Journal of Applied Physiology this month or next month.

Then below these daily measurements you have the 3-monthly measurements in the respiratory lab. Here you have the placebo and active, the annual change in the 2 groups, and this is the important data. You can remember what was on the left side, and the important result is that all these p values were far from significant, all the lung function p values, and we knew that from the beginning, that it would not be possible to see a difference between these groups because there were only 56 persons and 3-monthly measurements.

In fact, there was a slight advantage in the placebo group compared to the active group, and that is obviously chance. You can see that because you have negative values for FEV-1, and you have positive ones for TLC and RV, indicating that they are getting worse in the active group. Then you again have negative values for the diffusion capacity and constant, indicating that they are also getting worse in the actively treated group.

As a secondary measurement we did CT scans once again. This is a new principle so I just want to show some slides to make you more familiar with the idea of these CT measurements.

[Slide]

This is just to remind you that it has been long known, for a very long time, that the pathological problem in emphysema is disappearance of alveolar walls. Here, in the lower part we have the normal lung and this is the typical emphysematous lung where you can see that a lot of lung tissue has just disappeared.

The other very important thing to remember is that the x-rays are attenuated by density, by specific density of the tissue that it goes through, and that means that the Hounsfield numbers that you have in CT scans are, in fact, indicators of specific weight. Hounsfield did choose a misleading scale because he picked zero for specific density of 1 g/ml and minus 1000 for a specific density of zero. But you can easily transfer that into more understandable values.

[Slide]

This slide is just a topogram. The next slide will show you the slice at the carina level.

[Slide]

Here you have the ordinary way to present such a image. The problem is that you cannot really evaluate the degree of emphysema. It is all the black areas. But already 10 years ago Muller's group in Vancouver suggested the density mask method where you highlight all the blackest

pixels by turning them into white. He chose a threshold of minus 910 Hounsfield units because usually you won't have any pixels of that low value in normal lungs. Then suddenly you can see that half the lungs here are emphysematous in this patient.

[Slide]

This is taken from the newest textbook on pulmonary disease, Fishmann's textbook that came out this year. I think that illustrates the idea of this method. This shows how you can delineate the lung in such a CT image, and then you can make a frequency histogram of all the pixels of the lung, and you can see that most of the pixels have very low Hounsfield values. The nice thing about this illustration is that you can then highlight the low pixels and make a 3-dimensional reconstruction so that you can see the emphysematous areas of the lung. That is very valuable when you want to do lung reduction surgery.

[Slide]

Then you could ask why have we not used this measurement for many years when it is so obvious that it shows that it has something to with the emphysematous process. The reason for that is very simple, and that is that lung density is obviously very dependent on the amount of air in the lungs. Until now it has been very difficult to standardize the amount of air.

Then, the exceptional thing about our data is that we have serial CT data. I think nobody else has analyzed serial CT data before we did, and that means that we can now standardize the amount of air in the lungs. You can calculate the amount of air from the CT images, and this just shows that when you do calculate the volume of air in the lungs it has a good correlation to body box measurements.

[Slide]

If you do a deep breath from residual volume to total lung capacity, you can more than double the amount of air in the lungs, meaning that the density of the lungs will more than half. Therefore, it is extremely important to standardize the amount of air in the lungs. Here, this slide just shows that if you do CT measurements on the same patient -- each line here is a patient. He had 4 CT examinations in 4 consecutive years -- then you can see that the lung density, on the Y axis, is very dependent on the amount of air in the lungs. This amount varies quite a lot between examinations. Mathematically, when you have serial measurements, you can standardize the lung density back to a given volume for each patient.

[Slide]

When you do that, we found a very constant decline in lung density over a broad range of percentiles. This is,

again, a little bit technical so I think we will go on to the next slide. I don't have too much time.

[Slide]

Here you see lung function measurements on individual patients, yearly lung function measurements, FEV-1 and diffusion capacity, and on the same patients you have the CT lung density measurements. What you should be able to see from this slide is that the measurements here are more turbulent, more noisy, and you get a more stable picture when you calculate the lung density measurements.

[Slide]

That is, in fact, the same principle here. You only have the mean and standard deviations. That is much simpler to interpret. Here are the FEV-1 measurements of the placebo group, baseline, after 1 year, 3 years. You can see the decline in FEV-1 in the placebo group and in the treated group. As you see, the decline was larger in the treated group. This is the same with lung density and, again, the placebo group did better than the treated group. But the important message is that the standard deviations are very big and this is just a matter of chance probably.

Then you have comparable information taken from the CT measurements. Here you see a much more consistent development over the years. You have the years down here. This is the actively treated group, and the placebo group.

You see that it has the same tendency over the years and, very importantly, if you choose a slice, just one slice 5 cm below the carina, you will in fact have the same information. That is very important because then you can reduce the x-ray dose dramatically and CT is, in fact, combined with a quite large x-ray dose.

[Slide]

Then we can look at the CT data. Here you have the CT data in the lowest line, and what you can see is that the placebo group lost 2.5 g/L lung every year. The treated group lost less. They only lost 1.5 g/L lung tissue every year. That makes a difference of 1 g. The standard deviation of this difference is 0.5 g. So the p value, which is out here, was 0.07, which is not significant by traditional criteria but is close to significant.

So, the conclusion of our study is that we found that even the treated group did deteriorate. They lost lung tissue because this 1.5 g/L is significantly different from the normal, which is probably zero, no loss.

We did find a tendency of a difference between the treated and placebo group but that was not significant. Probably the most important result is that with the CT technique we probably have a method with which we can more precisely follow the progress of emphysema in these patients. It is more sensitive. It seems to be more

sensitive, and we may also believe that it is more specific because, as you know, FEV-1 is also changing in asthmatic patients and other lung diseases where the lung density will probably not change. Thank you.

DR. HOLLINGER: Thank you, Dr. Dirksen. The next topic is clinical trial design issues, Robert Stockley. Dr. Stockley is from Queen Elizabeth Hospital, in the United Kingdom. Dr. Stockley?

Clinical Trial Design Issues

DR. STOCKLEY: My major interest for many years has been COPD, and I have always looked upon alpha-1 antitrypsin deficiency as an accelerated version of the same problem. But I think as we are starting to understand the pathogenesis now, it is becoming quite clear that the pharmaceutical industry is interested in intervention studies, not just in alpha-1 antitrypsin deficiency but in other cases of COPD.

I think that the traditional outcome measure, the FEV-1, is really looking more and more like a non-starter for any type of phase II studies and probably even for alpha-1 antitrypsin deficiency. So, within Europe in particular, we have been looking over the past few years at other outcome measures and the way one might use these for clinical trials, and that is both in alpha-1 antitrypsin deficiency and general COPD. So, we have been in the very

fortunate position in that we have had unrestricted research grants from both Bayer and Glaxo to allow us to look at these two types of COPS in more detail, and try and get initial studies right because most of the trials have only one shot and if you get it wrong to start with, that is the end of a really good shot.

[Slide]

For my talk I have to cover an awful lot of things, and so I started by looking at what was available in the literature in terms of interventions that have already been tried in COPD, many of which have actually been accepted now as showing something and, of course, this is one which is well known, which is that long-term oxygen therapy does have a role in COPD, affecting mortality in patients who have, certainly in the U.K., cor pulmonale as one of the features of their COPD. So, that is a study which has been accepted, and a treatment which has been accepted worldwide even though it is quite expensive.

Beta-2 agonists have been shown to influence particularly the quality of life and morbidity in patients with COPD, as well as short-term changes in FEV-1. So, these two measures are going to be of importance in the patient and outcomes.

Then, of course, there is the role of antibiotics in exacerbations, and I am going to talk a little bit about

exacerbations later on because this is, I think, a mine field at the moment. But there are mixed views about whether or not antibiotics do have an effect in exacerbations of COPD. Certainly, response rate and cure and things like relapse rate are now actually coming into clinical studies.

[Slide]

Mortality is the easiest and I must say that now that I have actually seen the statistics I have become a little bit more concerned about mortality. I thought this was going to be something that we should pursue because it is clearly finite. We do know that mortality relates to lung function, and that has been used before as an outcome measure in long-term oxygen trials. Of course, as you have seen from Dr. Crystal, the NHLBI registry is very suggestive of an effect on mortality.

[Slide]

This just summarizes, of course, the two studies. the proper one done in the United Kingdom and the one done in the U.S.A. as an afterthought --

[Laughter]

-- but don't let that worry you right now. But basically the data is the same. Here is the mortality rate in patients receiving long-term oxygen therapy in the United Kingdom versus the control group receiving just general

medical care. Here is the similar data from the American study. So, I think that that is still potentially a way in which one could look.

[Slide]

Other interventions in COPD include things like steroid therapy. There are two ways of giving steroids. One is inhaled and one is oral steroids. There was a paper published in the Lancet recently suggesting that inhaled steroids may have an effect by producing less exacerbations over a period of 6 months. I think that data didn't quite reach statistical significance but needs to be pursued.

Steroids may influence the decline in FEV-1. Big controlled studies that have gone on in Europe are looking at that, and the data is being analyzed in a very similar way to the alpha-1 data.

In exacerbations that actually come in to hospital, steroids actually make the arterial oxygen tension rise more quickly. The FEV-1 rises more quickly and perhaps reduces the length of stay. Again, things that will be very important in outcome studies.

Then more recently, an interesting paper which I almost find it difficult to believe really was right, but people who swallow homogenized bacterial were found to have less exacerbations of COPD in terms of their hospital stay and the number of days that they had with their

exacerbations. So, again, a potential way of looking at outcome.

[Slide]

I think that you have already hear Asger Dirksen talk about high resolution CT scan and I am going to show you a little bit of the early data that we got on high resolution CT scan which I hope will support his views that careful analysis of this technique could be a very important way of looking at outcome.

We know that high resolution CT reflects the pathological change that occurs in emphysema. We know that it reflects to a greater or a lesser extent lung function in emphysema. I think from Asger's data, the impression that we are getting is that it may have less background noise than conventional ways of measuring pathology. And, we do know that the CT scan is going to be changing with time.

[Slide]

So, I will very briefly show you the same sort of data that Asger has shown you. This is a patient with alpha-1 antitrypsin deficiency. These black areas are relatively normal lung. This density mask analysis shows these great dilated air spaces which, of course, are not going to be taking part in gas exchange. That is an inspiratory film. So, the patient is taking a deep breath in and, of course, that will already give you more air in

the lung.

[Slide]

We have the same patient now on an expiratory film and, as you can see, the black areas are getting much greater and the white areas are less because, of course, you are getting rid of air that is within the lung in the normal tidal breath. But what you are doing now is retaining the trapped gas volume which in emphysematous areas can't empty very easily, enjoying normal tidal breathing.

[Slide]

So just to show a little bit of our preliminary data that we have been looking at in the patients with and without alpha-1 antitrypsin deficiency that are being studied within our program in the United Kingdom, on the vertical axis is the CT scan score. You heard Asger Dirksen talk about this measurement of minus 910 Hounsfield units as being a measure of the amount of air space enlargement. So, the higher this value, the more emphysematous change there is.

Here I have the lower zone of a group of patients in expiration and the lower zone in inspiration, looking at the relationship between this amount of emphysema by CT scan, and here the FEV-1, carried out post-bronchodilator, and that is bronchodilator with maximum doses of beta-2 agonists as well as anticholinergics -- so it shows, as you

can see, a reasonably good correlation, inverse correlation. So, the more normal your FEV-1 is, the less likely you are to have CT changes of emphysema.

Certainly on the expiratory film, I think it produces what you might expect, that when you breathe out people who have an FEV-1 around normal have virtually no change in CT score whereas, of course, when they breathe in it starts to come up here producing changes that might be conceived to be emphysema.

What is going to be important to us is analyzing the data the way that Asger does, and we are collaborating in this to try and get the same computer program to look at these CT scans his way as well. That is the FEV-1.

[Slide]

This is the other measure that we might think and talk about with emphysema, which is the gas transfer. Here we have expressed it as the KCO. This, in fact, is gas transfer per unit lung volume. So it is less variable than just using the total gas transfer.

Again, the CT score is up here. There is once again an inverse correlation. People with a normal KCO have virtually no evidence of emphysema and, as the KCO drops, up goes the measurement of air space enlargement, probably again better on expiratory films than it is on the inspiratory ones.

[Slide]

What I thought I would do is just show you the preliminary data that we have generated now on our first group of patients that have come up to 12 months analysis. This really just brings in what is being said. This is FEV-1 data, FEV-1 data over 1 year. It is a very variable technique. These are the patients who have actually had an increase in FEV-1 over a year; decrease in FEV-1 over a year, and it is just going up and down. Most of these changes are, of course, within the reproducibility of the test anyway. So, that suggests, as we all know, that FEV-1 is a difficult to measure if you are going to use it as your outcome.

[Slide]

This is the change in the CT score for our alpha-1 antitrypsin deficient subjects over the 12 months, looking at the upper zone of their lungs both at inspiration and expiration. Here, if there is progression of air space enlargement you would expect to see positive values, more areas of the lung which have holes in them. If it is getting better, if the lungs are repairing themselves, of course, you would expect it to come down this way.

Just looking at that data, you can see that the majority of these points are actually on the positive side of that, and the confidence limits for this are actually

greater than zero. So, at the moment, with just 12 months in the first way of doing it, without controlling inspiration and expiration specifically and accurately, it suggests, in fact, that we are seeing changes in our CT scan score.

[Slide]

The interesting thing is that if you actually take the same patients and you look at their change in KCO over that same 12 months, the KCO being gas exchanging units which would be interfered with in emphysema, you get the opposite trend. Here a positive result would be the KCO improving and a negative result being the KCO getting worse. Again, in this preliminary study the majority of these patients are actually showing a decrease in their KCO over the same period of time. The benefits we have here, of course, are that all these measurements are made by exactly the same group, in the same physiology lab, under the same conditions, which may, of course, be an advantage.

[Slide]

So with that as a background, I think high resolution CT scan does look really very promising, and I think Asger's data would also support that. What do we need in terms of validation before we actually use it? Clearly, we need to have a bit more information of reproducibility, which is something that we are actually doing at present in

our group.

It is going to be important that we not just compare CT scan to lung function but see what its relationship is to the quality of life of those patients and in particular their exercise capacity. Is it telling us something that is going to be important to the patient if you are going to try and intervene?

Then with all these things, how do they actually change with time? I think it is absolutely critical that before we do any major intervention studies we have our background information and our tests as accurate and as confident in them as we possibly can be because we won't be able to repeat these studies having made a mistake in our initial program.

[Slide]

So, the second thing that I have been asked to talk about is exacerbations. We know that exacerbations in COPD relate to mortality. We certainly know that an exacerbation is a bad time for a patient with impaired lung function relating to morbidity, and there is evidence that possibly, in fact, exacerbation may well be related to FEV-1 decline. So it is something that we should certainly look at and target.

[Slide]

It is interesting to listen to Mark's talk because

I think we are sort of coming at this from a slightly different angle but maybe with entirely the same lessons. What I would say is if you are looking at inflammation in the lung, it is not just a question of smoking; it is not just a question of pollution; it is not just a question of the degree of lung function, but it is a question for host defenses as well.

This is two slides of a set of three, and I haven't got the last slide up here, showing in very simple terms what is actually going on within the lung in host defense terms. Unfortunately, you can't see the bacteria but they are very, very small. So, when we inhale bacteria we know that normal host defenses will clear them. That is going to be the mucociliary escalator and resident phagocytes. There is now mounting evidence, for instance, that endotoxin from bacteria can act upon epithelial cells producing chemotractants such as IL-8. We also know that endotoxin acts on epithelial cells to produce a variety of pro-inflammatory cytokines, including things like interleukin-1, TNF-alpha, which have regulated adhesion molecules necessary for the inflammatory process.

You put these two together, with the phagocyte also contributing here to chemotractants and cytokines and you get a chemotractant gradient which disappears occasionally, and neutrophils become activated and

neutrophils start to move into the lung as the secondary host response. So, this is now when a patient is going to start to experience their exacerbation.

[Slide]

We then go through an amplification phase because just initiating it is not enough. You have to really now build it up, and there are a variety of pathways which are going to be involved here but I have just chosen a selective part of it. Here is the recruited neutrophil. It is inactivated neutrophil. It releases interleukin -8 and LTB4 in its own right. There is evidence which suggests that the elastase is released within the airway from the neutrophil, may act on epithelial cells and release even more interleukin-8 and, of course, you still have the drive from the bacteria. So, you now have a much bigger chemotractant gradient and more and more neutrophils coming to the lung. In a healthy person that is a self-limiting position so that eventually this all resolves and the patient gets better. In patients with chronic lung disease, unfortunately, that is not always the case and it may perpetuate.

[Slide]

We have been trying to look at this and understand what is going on in the lungs of patients with COPD for some two to three years. I think that we are probably starting to get a little bit close.

The first thing that we know is that many patients with COPD are actually already colonized with bacteria by the time they present in clinic. That is important because an exacerbation may be due to bacteria. So, there is going to be a difference between colonization and an exacerbation due to bacteria.

This is data that we have been doing in collaboration with Ed Campbell, looking on the vertical axis at a variety of measurements that we have made in lung secretions from patients, and relating these to the colonizing bacterial load that is present in the stable clinical state.

So, here we have patients who virtually have no colonizing load. This is mixed normal flora and no organisms identified at all in the secretions. Then 10^5 colony-forming units per ml, 10^6, 10^7, 10^8, 10^9 of a pure culture of a single organism. The data shows that in a stable clinical state there is a clear relationship between the cytokine content and this bacterial load. For instance, if you look at the yellow histograms, this is LTB4 showing LTB4 levels are high even when there is no load, but show progressive increase in concentrations as the bacterial load increases. Interleukin-8 here, in the red histogram, shows exactly the same sort of pattern. As you all obviously realized from Mark's data, this is myeloperoxidase which is

a measure of neutrophil infiltration, and neutrophil infiltration follows the same trend.

So, just having disease and bacterial colonization means you have an inflammatory process which is above and beyond what it should be anyway, and of course, that would apply both to alpha-1 antitrypsin deficient subjects as well as those without alpha-1 antitrypsin deficiency.

[Slide]

If we look at the thing that we all think is important, which is the elastase content, this is active elastase within secretions from patients with COPD, that tends to track with the myeloperoxidase. Again, this is colony-forming units -- more and more myeloperoxidase and as the neutrophil content goes up you start to find increasing concentrations of free neutrophil elastase which, of course, is going to be our potential target.

[Slide]

So with that as a background, exacerbations can obviously be of importance because bacteria cause exacerbations. The problem is that the definition of an exacerbation absolutely stinks. It is a very, very crude definition based upon a patient coming and telling you that they are not quite so good. So there may be many reasons why the patient is not quite so good. What we have been doing both in our clinic in Birmingham and also within

primary care is looking at exacerbations in COPD and saying, well, what the heck is an exacerbation?

You can see from this slide that what I have done is I have divided exacerbations into those that I call non-bacterial and those that I call bacterial. We can debate that issue in a minute but it involves proper analysis of the secretions produced before making a decision.

What I can tell you is that if you divide them into the two groups, you can see that the green histogram is the bacterial one and the yellow histogram is the non-bacterial one, and in this study on the vertical axis is C-reactive protein which is an acute phase protein. So, acute phase responses, as we have been talking about with alpha-1 antitrypsin, will be important in exacerbations. But it is only important in the exacerbations that I have called bacterial. In the ones that are non-bacterial C-reactive protein really hardly budges and, as you can see, remains pretty low throughout the treatment and recovery period, whereas in a bacterial exacerbation it is high and comes down with antibiotic therapy.

Just for those of you concerned about antibiotic therapy, all these ones here that I have put in yellow did not receive antibiotic therapy at all and they all got better. So, I think that we can come up with a way of dividing that up.

[Slide]

This is data from a much bigger study that we have done in primary care, looking at exactly the same way of dividing exacerbations. On the vertical axis again is C-reactive protein. You see that it is a log scale. So, these are patients with what we call a bacterial exacerbation at entry.

Here is the data at entry shooing they got raised CRP levels and it falls significantly down to a mean level here of about 6 mg/L or 7 mg/L in the stable clinical state when they got better.

The non-bacterial ones on this side have levels here at entry which you can see are very similar to the resolution ones here. In the stable state, in fact, there is a slight fall as these patients got better. Again, it would depend upon whether there has been perhaps a viral cause or some other minor inflammatory process with their exacerbation.

[Slide]

So, exacerbations can be a target but if they are going to be a target we need very clear definition of the cause of that exacerbation, a very clear idea of what effect it has on morbidity and healthcare problems. Above and beyond that, we need to relate these exacerbations to the actual clinical state. Patients with COPD and alpha-1

antitrypsin deficiency do or don't have bronchitis. They do or don't have bronchiectasis. They do or don't have physiological impairment and, of course, they do or don't have high resolution CT changes.

[Slide]

My final slides are just going to run through other potential markers that we have thought about, and many people have thought about with reference to intervention studies in COPD and alpha-1 antitrypsin deficiency. There are, of course, the biochemical markers. In alpha-1 antitrypsin deficiency certainly alpha-1 antitrypsin is an easy marker. You can show it is low; you can show it goes up. That doesn't necessarily mean that you are doing anything positive to the patient.

We can measure the proteolytic enzymes themselves, looking at their activity or surrogate markers for that activity, and I think that is probably going to be of more importance, trying to track surrogate markers.

We can look at the inflammatory process but, as I think you will have gathered from both the data that Mark has been showing and the data that we have shown here, this is a very complex process which involves many different facets and trigger points. So, we have to be quite clear what the inflammatory process is related to before we can really use it.

Then, of course, there are things like elastin degradation products which I think the jury is still out on. It has so far been quite disappointing as a way of tracking things. But, again, within Europe there is currently a study going on between Maurizio Luisetti's group and Gordon Snider's group looking at this particularly in alpha-1 antitrypsin deficiency and relating it to replacement.

[Slide]

Other biochemical markers -- we do need to validate them by their reproducibility, by their relationship to physiology, radiology, and by the clinical features that we are dealing with, and we do need to know what their background change with time is before we can actually power up an intervention study.

[Slide]

Quality of life is the most important thing to the patient. The patient, unless they really are specifically neurotic, is not interested in what their alpha-1 antitrypsin level is today, yesterday or the day before. They are interested in their quality of life. Can they do things? Is their morbidity bad?

So, we know the quality of life relates to the severity of the disease, but the quality of life tools that we use at the moment are really not sensitive enough for the type of intervention studies that we do. So, they really do

need to be developed, new sensitive tools that are going to tell us what it is we expect to find. Clearly, we need to validate it with high resolution CT scanning, lung function testing, and particularly with exercise, how much the patient can actually do, in a very specific and controlled way.

[Slide]

That comes back to activity which, of course, is the other side of it. What can the patient actually physically do? We need to develop refined tests, like the incremental shuttle-walk test and again look at the reproducibility and validate them against all these other aspects.

[Slide]

In Europe we take this very seriously and we have a long-term aim, and the long-term aim has been helped by the fact that we actually now do talk to each other in greater detail and we have established, as you can see, a group of international registries for alpha-1 antitrypsin deficiencies. Here are the countries that are actually involved in this, meeting on a regular basis. We are moving forward tentatively but very positively.

We have now established a common database which will be for all registries, held in Mamo, in Sweden by Sten Eriksen. That is only fair since he discovered it in the

first place. Currently, we have in excess of 4000 patients from these registries. This is increasing monthly. And, I think it is important to emphasize that in Europe, with the exception of Germany where patients are receiving augmentation therapy, the vast majority of our patients are not on augmentation therapy. Thank you.

DR. HOLLINGER: Thank you very much, Dr. Stockley. The final talk this morning is on epidemiology perspective, by Dr. Edward Campbell from the University of Utah. I remember when we were looking at Rice basketball program one time, and they were playing UTEP, which is the University of Texas at El Paso, and they had UTSA, the University of Texas at San Antonio, and they had "UTAH," and we kept thinking, "University of Texas -- where?"

[Laughter]

And then we recognized it as Utah versus Texas at Houston.

Epidemiology Perspective

DR. CAMPBELL: I don't know how to respond to that! Mr. Chairman, thank you very much for giving me the opportunity to address this group this morning. Ladies and gentlemen, good morning.

[Slide]

Let me make three introductory points, the first being that alpha-1 antitrypsin deficiency is defined

biochemically requiring a level of circulating alpha-1 antitrypsin of 11 microM or less. More than 96% of all individuals with alpha-1 antitrypsin deficiency have phenotype Pi Z, and have only the Z variant protein in the circulation. Individuals with the Pi SZ phenotype, which has been referred to this morning as a compound heterozygote, have 1 allele for the Z variant and 1 allele for the S variant. For this reason, they express both the S and Z gene products in circulation, and they have moderately reduced circulating alpha-1 antitrypsin. For the purpose of this discussion, we can consider them to be very useful experiments of nature.

[Slide]

Dr. Pierce, in his introductory remarks this morning, made some comments about undetected antitrypsin deficiency. I would like to contrast the situation that now exists with antitrypsin deficiency to that which exists with cystic fibrosis. In cystic fibrosis, with regard to the prevalence, it occurs about once in every 2500 live births. The median survival now approaches 40 years. About 23,000 living patients now exist in the United States, according the CF Foundation data. Of those 23,000, the Cystic Fibrosis Foundation actively follows 20,000 patients in 114 clinical centers in the United States. Since most of those patients are known and actively followed in an organized

way, we have a very clear understanding of the natural history of cystic fibrosis.

In contrast, alpha-1 antitrypsin-deficiency occurs in at least 1 in 2750 individuals in the United States. There are more than 80,000 living patients in the United States. But only a few thousand of these have been diagnosed. It was difficult to find the 1000-plus patients enrolled in the national registry, and now a little more than 2500 patients are receiving augmentation in the United States. From registry data, we would expect this to be about 60-70% of those diagnosed.

So, I estimate that at a maximum about 4000 patients in the United States have been diagnosed out of the more than 80,000 living patients. So, we know very little about what the remainder of the undiagnosed patients with alpha-1 antitrypsin-deficiency look like, whether they are sick or healthy; whether they are seeing doctors, not seeing doctors; whether they are being misdiagnosed or not misdiagnosed. So, it is a major problem that exists with our understanding of this disease today.

[Slide]

Dr. Pierce asked me to comment on risk for lung disease in Pi SZ heterozygotes for alpha-1 antitrypsin-deficiency. I want to emphasize foremost that the exact risk to these individuals is unknown. This is particularly

true because the knowledge of the natural history of these individuals suffers from severe ascertainment bias. In many of the known Pi SZ individuals had been identified because they presented with lung disease. So, if we only test for alpha-1 antitrypsin deficiency in individuals who present with lung disease, the only people that we identify as being Pi SZ heterozygotes have lung disease.

The British Thoracic Association, in 1983, reported a series of individuals with Pi SZ phenotype, and in summary, their conclusion was that there was little or no extra risk of emphysema due to the Pi SZ phenotype.

The data published by the NIH registry, in 1996, of which Dr. Turino was the first author, I read somewhat differently from previous speakers this morning. I think the conclusion is best stated, and this is a quote from the paper itself, there is little or no added risk of developing COPD in the Pi SZ heterozygotes.

[Slide]

This slide shows data on alpha-1 antitrypsin levels on the vertical axis, here, grouped by phenotype. So, in this graph the reference value of 32.4 microM is what we accept as normal. The 4 groups on the left are various heterozygotes for alpha-1 antitrypsin deficiency who have minimal, if any, excess risk of developing lung disease. These include Pi MS, Pi S, Pi MZ and Pi SZ phenotypes.

What I think you can appreciate is that although the mean level in these individuals is less than the reference value, all have plasma values, with only 2 exceptions that I will get to, which exceed 11 microM. In contrast, you can see the levels in the Pi Z individuals who have alpha-1 antitrypsin deficiency are much lower and have levels in all cases less than 11.

So, the conclusions that we draw are that the mean plasma level for Pi SZ individuals is 17.7 microM, and among 244 Pi SZ individuals that we tested only 2 had levels of less than 11. Those levels in those individuals were 10.9 and 9.8.

Among 744 pi Z individuals the highest level was 10.6. So, the 11 microM level in our hands does provide a striking, very clear separation between the various heterozygotes who are at minimal, if any, risk of excess risk of lung disease in alpha-1 antitrypsin-deficient individuals.

[Slide]

It is interesting to note that the levels in Pi SZ heterozygotes do to some extent span the 11 microM threshold value which has been spoken about this morning. In the NIH registry 10/15 Pi SZ individuals had levels of 11 microM or less. These individuals had actually a lower prevalence of cough and wheezing with respiratory infections, and less

severe lung function impairment.

With regard to the lung function impairment, we will look only at the FEV-1 and compare the Pi SZ individuals with levels of 11 microM or less with those having levels of greater than 11 microM. FEV-1 in individuals with the lower strata of alpha-1 antitrypsin levels was significantly better than those with the higher levels.

So, that leads me to conclude that there is no evidence of a higher risk of symptoms of lung function impairment in Pi SZ individuals with levels less than or equal to 11 microM. An opposite trend in this study suggests only that the Pi SZ subjects who are ill can mount an acute phase response and increase their alpha-1 antitrypsin serum levels.

[Slide]

Traditional hands-on kinetics provide a fairly poor explanation for the risk of lung disease in people who have alpha-1 antitrypsin-deficiency. So we have been interested in trying to develop a different construct for understanding tissue injury in alpha-1 antitrypsin deficiency. What we have focused on is looking at the consequences in immediate vicinity of activated neutrophil or white blood cell of the release of single granules that contain elastase.

[Slide]

This slide shows that neutrophils, white blood cells, which I have here abbreviated PMN, are incubated on fluorescent fibronectin so that we can see it through the microscope. That is overlaid with anti-fibronectin IgG to give the neutrophils something to hold onto. Neutrophils were introduced onto this flat surface while bathed in serum from individuals with known phenotypes for alpha-1 antitrypsin deficiency, and the proteolytic events that result from single azurophilic granule release are imaged.

[Slide]

This slide shows a microscopic image of neutrophils that are bathed in serum from normal individuals with Pi M phenotype. This neutrophil landed on this spot and degraded fibronectin as it went along during the course of this assay, and ended up here. The alpha-1 antitrypsin in the patients' serum protected all of the fibronectin in this white area around the cells. It was unable to protect the fibronectin beneath the cells.

What I hope you can appreciate is that there are very discrete little areas of degree in fibronectin which each result from release from a single azurophilic granule.

[Slide]

This slide shows the same image that you just saw on the left panel, and contrasts it with the image from a

neutrophil from the same individual but it is now bathed in serum from a patient with alpha-1 antitrypsin deficiency.

What you can, I hope, appreciate is a striking difference in the size of these single events on the left side with this one event that we are looking at in the image on the right panel. Since the events are much larger in patients with alpha-1 antitrypsin deficiency, we have to be lucky to find single isolated events. But I think you can appreciate the path taken by this neutrophil. It has lumpy, bumpy borders with radii similar to this.

We are able to measure the radius of these events with our instrumentation, and the mean radius in the events in this panel was a little over 1 micron and nearly 6 from the patient with alpha-1 antitrypsin deficiency.

[Slide]

This shows some quantitative data resulting from experiments like the one that I just showed. It shows the size of these proteolytic events as a function of the plasma alpha-1 antitrypsin level, and the data here are grouped by alpha-1 antitrypsin phenotype. The heights of the bars are the area in square microns of the events that we imaged, and various bars are different alpha-1 antitrypsin phenotypes. On the right is a normal or M phenotype, and MS, MZ and SZ phenotypes.

I think what you can appreciate is that although

the heterozygotes have slightly and statistically significantly increased size of these events, the biological significance is questionable. In contrast, patients with alpha-1 antitrypsin deficiency have much greater size of these events even in comparison with Pi SZ individuals.

So, we conclude that neutrophils in serum from individuals with normal and heterozygous phenotypes produce similar event sizes but neutrophils in serum from Pi Z or alpha-1 antitrypsin-deficient individuals produce markedly different event sizes that are highly significantly different from all the remaining phenotypes.

[Slide]

With regard to the basic science evidence that I have just shown, we conclude that quantum proteolytic events produced by neutrophils resulting from single azurophil granule release are abnormally large and prolonged in individuals with alpha-1 antitrypsin-deficiency. Abnormality is minimal in heterozygotes even in individuals with the Pi SZ phenotype. This abnormality leads directly to an increased risk of tissue injury in the immediate vicinity of activated neutrophils. We believe that these results and concepts have important implications for the pathogenesis and therapy of lung disease in alpha-1 antitrypsin deficiency.

[Slide]

Dr. Pierce asked me to comment on the quality and precision of data supporting the 11 microM endpoint for augmentation therapy. I want to make several points in that regard. First, all of us have to admit that the 11 microM level was chosen arbitrarily. It does exclude, as we have seen, most Pi SZ heterozygotes who have minimal, if any, increased risk of lung disease.

However, we must realize that the 11 microM does not divide the Pi SZ individuals into high and low risk subgroups when individuals are stratified as being greater or less than 11 microM serum level.

Dr. Crystal showed us this morning that the concentration of circulating alpha-1 antitrypsin in individuals undergoing augmentation is extremely dynamic. It is actually higher than normal for approximately 2 days, and there are no data leading to the conclusion that the 11 microM trough level is critical. That would require us to believe that important and critical amounts of lung injury occur in the hours to a day prior to subsequent infusion.

[Slide]

I will try to illustrate that on this slide.

DR. HOLLINGER: Dr. Campbell, could you perhaps get to the conclusions of your presentation because we are running out of time?

DR. CAMPBELL: Yes, sir. I think you can

appreciate that these levels are quite dynamic, and the 11 microM threshold is here. So, most of the week in individuals getting weekly augmentation, the levels are actually much higher.

[Slide]

Basic science theory and experimentation I have shown you indicates the 11 microM level is approximately correct but does not provide an exact endpoint. Products used for augmentation are not fully active unless the circulating level of 11 microM is not functionally equivalent to an 11 microM level of endogenous alpha-1 antitrypsin. We have already heard that in normal individuals alpha-1 antitrypsin is an acute phase reactant and there may be a benefit to higher levels during acute respiratory illnesses and systemic infections or stresses.

[Slide]

Best available evidence suggests that augmentation as currently prescribed, with the goal of achieving a trough serum level of 11 microM does have benefit. I want to emphasize that there is a worldwide shortage of product. The currently accepted goal of an 11 microM trough concentration is reasonable although arbitrary, and should be accepted, in my opinion, as a standard of phase III trials. Importantly, attempting to define a more exact biochemical endpoint at this moment in time is clinically

impossible.

[Slide]

So, my conclusions are that phase IV studies and not phase III should focus on timing of augmentation for alpha-1 antitrypsin deficiency development and validation of efficacy measures other than circulating alpha-1 antitrypsin levels, for which we have none at the moment. And, such phase IV studies can be expected to have a substantial beneficial impact on the management of the disease state. Thank you for your attention.

DR. HOLLINGER: Thank you very much. Dr. Smallwood has a few comments and then we will take a break.

DR. SMALLWOOD: Yes, I would just like to advise those sponsors that are presenting in the open public hearing, at the beginning of the break would you see the gentleman at the back, Mr. Wilchek, regarding your slides, if you have not already seen him? And, if you have any overheads, Miss McMillan will be able to help you. This is to facilitate a smooth presentation. Thank you very much.

DR. HOLLINGER: We will take a break until 10:25.

[Brief recess]

Open Public Hearing

Alpha-1 National Association

DR. HOLLINGER: There are four companies that have asked to speak in the open public hearing. They have been

given a time limit for their discussions of ten minutes. The first individual who has asked to speak is from the Alpha One Foundation, John Walsh, and we would like him to come forward, if he would, please.

MR. WALSH: Thank you, Mr. Chairman; thank you, Dr. Smallwood. I apologize for the delay in the schedule.

[Slide]

I have been asked to present the patient's perspective today on the review of clinical trials for alpha-1 antitrypsin deficiency. We don't use the "P" word very often. We are called in-patient patients. We refer to ourselves as consumers more often than patients.

[Slide]

But currently, because of the critical shortage of alpha-1 anti-protease inhibitor product Prolastin, unfortunately, a greater majority of our community are, indeed, patients at this time.

[Slide]

I am going to try and cover in ten minutes the patient perspective, which will include an overview of the alpha-1 protease inhibitor background and experience with Prolastin specifically; the critical product shortage and its effect on our attitude about clinical trials, as well as the product itself; the increased awareness and detection that has been established over the past 10 or 11 years,

which definitely increases demand for the product; the limited alternatives that we have available because of the limited number of people we have diagnosed; the limited emphasis on research and development of products; and alternative therapy strategies; and also our community commitment and challenge looking forward, not backward.

[Slide]

Just as a background of alpha-1 P, you have heard Ron Crystal eloquently express and report on the data from the NIH registry, the 7-year longitudinal disease progression study. In 1985, 21 patients were recruited from our community to establish the biochemical efficacy if alpha-1 PI. In 1987, thanks to the leadership of Ron Crustal and others at NHLBI and the FDA, alpha-1 protease inhibitor product Prolastin was approved, and under the orphan drug statute, was produced by Bayer, soon to be Miles and not Bayer. And, we are glad that those three entities, the FDA, the NHLBI and industry, took the leadership role in making certain that the patients had a therapy available to us that would help us deal with our disease.

In 1989-92 1129 patients were identified across the country and participated in a 7-year longitudinal disease progression study. Today is the first time any patients -- and I have Julie Swanson, president of the Alpha One National Association, Joe Riedy, a member of the Alpha

One National Association and fellow alpha patient, as well as Sandy Brantley, Executive Director of the National Association, here with me today -- this is the first time we hear data presented in an official capacity and we look forward to the final publication this month of the registry report.

[Slide]

Our experience with augmentation therapy is direct. I, myself, infuse weekly Prolastin, as does Julie Swanson. Most people are home-infused, and about a third of our infused population are being infused in clinics and physicians' offices because HCFA does not approve home infusion.

The NIH trial established for our patient community that, number one, there was interest in NHLBI in developing therapies. Number two, there was industry reaction and response. They saw a market opportunity to sell therapies to us and, in turn, it has created a considerable higher level of awareness about alpha-1 antitrypsin deficiency.

We had reimbursement challenges initially. It took me personally three years to get on product. We fought the insurance companies head on. They approved product based on the physician support and the strong support from industry. We believe as the patient population -- Ron

Crystal referred to it as "acts like a talk, talks like a duck, walks like a duck." We are the duck. And, we do believe that augmentation therapies work, and we will talk about that in more detail. We do not, however, embrace the thought that we are fixed. We need to optimize the therapy. We need to look at other alternative delivery strategies, and we need to develop new therapies that will help us even more.

There is no question that if you line 100 alphas up that are currently on augmentation therapy that they will tell you that they have had fewer infections, some none; fewer hospitalizations, most none; and that we have had much higher or better quality of life as a result of being on augmentation therapy. That about says it all. That is anecdotal, but from the patient perspective the most important thing for us is to stay healthy as long as we can so that we can support our families, stay in the work force, and live longer.

Increased understanding and awareness about alpha-1 deficiency and detection is a challenge for us. We are a small community. You heard Ed Campbell present data that we have the same prevalence as cystic fibrosis in the general population. We have identified less than 5000 patients. We have 85,000 to 100,000 left to go. Detection is a critical issue for us. I wish this Committee was addressing the

medical devices application, but there is a Hereditest, a finger-stick test that was developed by Ed Campbell that we need desperately to be able to diagnose people.

We firmly believe that a strong detection and diagnosis program is critical at this time in our community even with the shortage of augmentation therapy because of the fact that the sooner you know what you have to deal with, the sooner you can take appropriate actions. Our physicians have developed several levels of reaction to some of the exacerbations that we have -- aggressive treatment of infections, pneumococcal vaccines for the whole family, annual flu shots. It is clear that exercise and nutrition improve our quality of life, and we need to focus on those activities and learn more about those as well, in addition to making certain we have more product available for augmentation therapy.

[Slide]

The support for the benefit and use of augmentation therapy -- we are just simple patients but we are a relatively sophisticated community; we are all middle-aged. We are not symptomatic until we are 35-45. We want to live longer. We don't want to give up the quality of life we have reached at this time in our lives. The approval of alpha-1 by the FDA, the government if you will, the attention by the NHLBI and our experience over ten years

establishes that the community, the industry and the government has embraced that augmentation therapy is relevant. HCFA is treating some 600 to 800 alphas currently and supporting their therapy. The survival data, mortality data and morbidity data, the FEV-1 data that is being published this month from the NIH registry establishes or conveys that there is a benefit for at least some portion of those people on augmentation therapy, and it shows. What doesn't show is where there wasn't benefit or there wasn't the benefit for each and every person that is less than 35% of predicted. Clearly, they have had fewer infections, and had fewer hospitalizations, and are living a better quality of life.

There are three other studies that have been done. The Danish-German study -- Marian Wencher is here from Germany and you heard Asger Dirksen earlier -- they had 97 in the Danish, 198 on the German side, ex-smokers. Germans had uagmentation therapy, the Danes didn't. The rate of decline conveyed a specific benefit for augmentation therapy. That is in black and white. I am not a scientist but I am a patient with the ability to read, and that is our perspective.

The German study, with 323, done by Marian Wencher and her associates, showed fewer bronchitic episodes. Right now, what more can we ask for besides feeling better and

living longer?

The U.S. patient experience, as discussed by Ron Crystal, again shows that there is a demonstrated obvious benefit to augmentation therapy. There are no alternative therapies. The only alternative we have is to get our alpha docs to make certain that we do the right things and stay as healthy as we can, as long as we can.

[Slide]

The effects of Prolastin shortage --

DR. HOLLINGER: You have a minute.

MR. WALSH: The Prolastin shortage has had a tremendous effect, in our opinion, on therapy and we need to focus on the fact that we need product. The patient community has a balancing act here. The balancing act is between the science and availability.

We certainly want more studies done with respect to dosing studies, maybe a 60-, 90- and 120-day study concurrent with but not to inhibit availability of product, slow down the availability of product. We are opposed to demanding efficacy trials that will stop Alpha Therapeutics from their product development. We need their product approved and we need their factory certified. The Centeon study needs to be approved. We need more product. The effects of a one-supplier product in the market like ours is devastating. We are on a 50% allocation now. That is, our

patients are not getting enough product. There are people missing their windows for lung transplantation because they are getting sick, and there are people that don't have enough product. Over 600 people aren't getting product that were on product.

So, we need your help and we ask this Committee to please address the issues of availability and balance them with science. We are not opposed to science and further exploration, and we need product, first and foremost. Thank you and I am sorry I didn't go through all of my slides, Mr. Chairman.

DR. HOLLINGER: Thank you, Mr. Walsh. I don't want to feel like an ogre about this time but, you know, if we don't watch our time we will be here until very late, and we have a very full time commitment here. We told everybody how much time they have so we are going to stick with it. So, give your best shot in the time that you have. If there are things that have been covered before, then let's not see them again. The next is from Alpha Therapeutics.

Alpha Therapeutic Corporation

DR. VERDUYN: Good morning, ladies and gentlemen.

[Slide]

I am Carin Verduyn. I am the clinical director for Alpha Therapeutic corporation, in Los Angeles, and in the next ten minutes I will give you a brief overview of the

clinical trial that has been done in congenital alpha-1 proteinase inhibitor deficiency. This study is sponsored by Alpha Therapeutic and has been closely developed with the FDA, and should form the basis for a PLA submission at the end of the year.

[Slide]

The study was started in March of '97. The study required 24 evaluable patients and was a multicenter, randomized, double-blind, active controlled, phase III study. The objective was to demonstrate efficacy and safety of alpha-1 PI in patients with this congenital disease.

[Slide]

Once the patients were selected and enrolled, they were randomized into two groups. One group received active control and the other group received active treatment, which is alpha-1 PI. Both groups received the treatment in doses of 60 mg/kg in weekly infusions for a total of 10 weeks, and at week 11 all patients received alpha-1 PI, for a follow up out to 24 months.

Between week 7 and week 10 the first batch of clinical assessments that were important for study endpoints were made, and again between weeks 11 and weeks 24. I will come back to these clinical assessments in a minute.

[Slide]

There are two primary endpoints. One is to

demonstrate equivalence treatment groups of mean serum alpha-1 PI trough levels during weeks 7 through 10, and the other is to determine that the serum alpha-1 PI trough levels for all patients are maintained during weeks 11 through 24.

[Slide]

The secondary endpoints are to determine equivalence between the treatment groups of serum and anti-neutrophil elastase capacity during weeks 7 and 10. Further, we look at mean change from baseline after 6 weeks treatment of alpha-1 PI and we look at the trough alpha-1 PI levels and anti-NE capacity in the serum as well as in the BAL fluid.

[Slide]

The other assessments relate to possible long-term effects on pulmonary function and x-ray morphology, and the biochemical determination of the degradation products and biological half-life have also been included.

[Slide]

In the interest of time, I will only briefly go through the main inclusion and exclusion criteria. Patients were included if they had congenital alpha-1 PI deficiency, as well as signs and symptoms of emphysema and low level of alpha-1 PI in the serum. The FEV-1s were between 30% and 80% predicted.

[Slide]

And, patients were excluded if they had previous augmentation therapy in the previous 6 months and an abnormal blood gas analysis. Because this is a safety study, patients who had antibodies for hepatitis or for HIV were excluded.

[Slide]

There are a number of procedures throughout the study, and this is the list of procedures that are done at the study start. You will notice that patients are subjected to BALs and they have arterial blood gas draws. The alpha-1 PI level and the anti-NE capacity determinations are performed at Dr. Brantly's laboratory.

[Slide]

These are the procedures and assessments that are done throughout the study each week, and again you will notice that the alpha-1 and anti-NE capacity determinations are done weekly.

[Slide]

These are the procedures that are done at designated times throughout the study. You will notice that at week 7 patients undergo another BAL.

[Slide]

The status thus far -- 26 patients have actually been treated throughout the double-blind period at 4 sites

throughout the United States. This is a list of the investigators who have participated.

[Slide]

Twenty patients have already been treated throughout the 6-month treatment period. Of the 26 patients, all are white and most of them are male. They are middle aged. Most of the patients are ZZ phenotypes, bar 1. From the lung functions we can see that most of the patients have severe lung function impairment.

[Slide]

The study is at present still blinded. So, we can look at clinical results for all patients. You will notice that the mean trough alpha-1 PI serum level has substantially increased between baseline and seek 7. The 16.6 is obviously a lot higher than the 11 threshold level that we have been talking about. At week 7 all patients had a blood serum level above 11 microM.

In this group of patients we have not been able to detect a difference in the lung function tests between baseline and week 7, as can be seen by this FEV-1 percent predicted. This is basically in line with previous publications on alpha-1 PI.

[Slide]

Looking at the data on adverse events that are possibly, probably or definitely related to drug treatment,

we can say that as a whole the patients tolerated the treatment well. Up till now 950 infusions have been given to the patients, and any adverse events that did occur were generally in the mild category. This one moderate adverse event represents pruritus 3 days after infusion.

[Slide]

In summary, we can say that this is an ongoing, long-term, well-controlled study with a minimum of 24 evaluable patients; 26 patients have been enrolled thus far. The mean alpha-1 PI serum level was above 11 microM level. From the preliminary data, we can say that augmentation therapy is safe and feasible. All patients will have received their weekly treatment for 6 months during August. So the data on 6-month treatment could be available after September, 1998.

I thank you for this opportunity to inform you of this important study.

DR. HOLLINGER: Thank you very much. The next presentation will be by Bayer.

Bayer Corporation

MS. SPENCER: Hello. I am David Spencer, from Bayer Corporation. I am in charge of international product development for plasma projects, and I appreciate the chance to tell you a little bit about our supply situation today. We were asked to address that because we are in the midst of

a shortage, and I think it is important to inform you where we are with Prolastin supplies.

[Slide]

This goes through some of the history of the situation that we have had. I will show a history slide in a moment on our production, but we have been looking for ways over the years on how to continually improve production of this product. The improvements that we have already identified came together with an inspection that we had with the FDA towards the end of 1997. Team Biologics was really able to help us identify some further improvements. So, we targeted installing those in our filling line for Prolastin, as well as for other products.

Unfortunately, at the same time we had an unanticipated failure in our heating, ventilation and air conditioning system that is connecting with that filling line. So, we had a production disruption at our main plasma products manufacturing facility, which is in Clayton, North Carolina.

Now, that didn't cause base fractionation to stop but it did cause us to have a disruption in the filling and finishing of these products. So, for some of our plasma products, and Prolastin is one of those, we also have the capability to fill and finish in our Berkeley facility, which is primarily dedicated to the production of cogenate

for hemophilia. So, we shifted the capacity that we could to Berkeley during this time period. We have actually finished all of the changes to our filling lines and we are basically waiting for approval to release product that in the meantime has been finished in Clayton.

[Slide]

This gives an overview of the process, and I am not going to try to give you a quick course in plasma production. I would just like to point out that the top line is the backbone of the cone fractionation process, and we start to purify our product from a fraction called 4-1. From there, the purification process goes on. We also have two viral inactivation steps in here.

But if you keep in individuals that there is also at least 60 days we have inventory hold and lookback possibilities before plasma enters the facility, and that this entire process takes on the order of 120 days, and then we have some time after that for release and shipment, we are looking at nearly 200 days from the donor to final product that is available. That is important because not only is one not able to turn on a dime when something happens here, but if there are any observations in the facility, even towards the end of this production process, that can make you hold the lot to lookback, check all your environmental monitoring data and make sure that everything

is okay before you release the product.

So, that means that there is a certain amount of unpredictability in being really able to tell lot by lot when the next amount is coming out.

[Slide]

Now, if we look over the last years, what I have done here is to index the 1997 supply to the U.S. market and call that 100%. So, you see that I didn't go all the way back to 1987, but you can see that we have had a steady increase in availability. So we have really tried consistently to do what we can to increase the amount of plasma that we fractionate, as well as to increase our ability to purify this particular very important product.

Fortunately, it looks like despite the problems that we have had in the first couple of quarters of this year, we are going to be able to finish the year at about where we were last year.

[Slide]

The reason that we have a 50% allocation right now has been simply the unpredictability of the supply. This gives you some feel for how we have been releasing product. As a matter of fact, the only reason March was this high was because this was the last amount of Clayton-filled product from 1997 that we were able to release this year. All the rest of this, from January to May, is from Berkeley, and

that only has about 30% of our total capacity to purify this product. So, the anticipated June releases already anticipate that we get final approval for the changes that we have made to our filling lines in Clayton, and that product that we have been producing for the last couple of months can then start to be released to the market.

[Slide]

So, the product is on allocation. We initiated that mid-January, and we did this in interaction with the Alpha Patient Association because we didn't want to have a situation where there were boluses of material coming out and then there were stretches of absolutely nothing. So, we are trying to avoid out-of-stock situations. We had to base our allocation on historic customer purchases.

[Slide]

But assuming that the approval of the filling line changes occur this month, we are looking at a very good third quarter, which will be a little bit offset by the fourth quarter. So, in general I would just like to say that I think the Prolastin production is coming back on. If these releases come out the way we anticipate, I think that in mid to late July we will probably be able to modify the allocation program. But I think this also emphasizes the importance of balancing research and supply, like John said. We have to make sure that we take care of job one, get the

product out there and serve the patients, and then support the kind of clinical research that we have done in the past and we are continuing to do, but do it responsibly with the right product amounts. That is all. Thank you very much.

DR. HOLLINGER: We have just a couple of minutes. Does anybody on the Committee have a question for our speaker right now? Yes?

DR. KOERPER: I have heard rumors that some of the product is going to Germany. Can you comment on that? What percentage, etc.?

MR. SPENCER: Last year about a quarter of our product went to Germany -- sorry, not just to Germany, to Europe. It is primarily Germany, Spain, Austria to some extent. That is a result of a historic growth because we have started to work with patient groups in these countries ever since 1987. So, that has developed historically, and we have patients in Europe that very much depend on this product, just like in the United States.

That being said, the fact that we had to depend on our Berkeley facility so much this year, which is not licensed in Europe, has meant that far less product on a percent basis is going to Europe this year. Far more of it is going to the U.S.

DR. KOERPER: And since Bayer is a German company, are there any plans for them to start producing it in

Europe?

MR. SPENCER: We have really tried to treat every single market even-handedly. So, the problems that have kept us from sending to Europe we have been addressing just like we have been addressing the problems that have kept our total amount low. I believe that actually in July we will start shipping again, but I think it will really pick up more in August and September towards Europe. But that being so, there is still going to be, on a percent basis, more in the United States than there was last year.

DR. HOLLINGER: The time from cone fractionation until you release the product is how long?

MR. SPENCER: It is 120 days.

DR. HOLLINGER: Thank you.

DR. KOERPER: Also, what are your viral inactivation steps?

MR. SPENCER: They are heat and solvent detergent.

DR. KOERPER: Heat at what time and temperature?

MR. SPENCER: Dry heat, 80 degrees.

DR. KOERPER: For?

MR. SPENCER: Six hours, I believe. I am sorry, I need to check that. We have done viral validation on the steps. If you know heat, you know that it is quite variable in terms of its efficacy. It depends on what excipients you use. It depends on what moisture levels you have. So, we

have looked very closely at the exact conditions to make sure that in all our model viruses we were getting efficacy in that step, and we have submitted that data to the FDA as well.

DR. HOLLINGER: Thank you very much. The next presentation is by Centeon.

Centeon

DR. BRYANT: Good morning. I am Dr. Christopher Bryant, from Centeon, and it is my pleasure to be able to present Centeon's A-1 proteinase inhibitor program today.

[Slide]

Centeon's A-1 PI program is designed to provide an effective, high quality therapy to patients with alpha-1 antitrypsin deficiency as quickly as possible. We hope to partner with government agencies in responding to the needs of the patients and medical communities.

[Slide]

Toward these program goals, we have developed a high purity product with up to 98% monomer in the final preparation, as demonstrated in the following HPLC chromatogram.

Furthermore, the manufacturing process for this product incorporates 2 complementary steps for the reduction of possible blood-borne pathogens, including pasteurization and nanofiltration.

[Slide]

We seek approval for our product for the indication of chronic replacement therapy for individuals with congenital deficiency of alpha-1 proteinase inhibitor and emphysema at a dose of 60 mg/kg/week, as approved for the currently licensed product.

[Slide]

Centeon's clinical development program consists of 4 clinical studies, 2 completed supportive studies and 2 planned pivotal studies. I will initially describe data collected during the completed supportive studies and will follow with a description of our proposed pivotal studies.

[Slide]

The first of these studies is a phase I single-dose pharmacokinetic study including doses up to 120 mg/kg. Some of that data was shared by Dr. Pierce this morning. The pharmacokinetic profile obtained in this study predicts that weekly administration of 60 mg/kg functional A-1 PI will result in serum A-1 PI levels above the historically accepted protective threshold of 11 microM discussed here today.

The second completed study is was a phase II open-label safety and biochemical efficacy study. It involved weekly A-1 PI infusions at 60 mg/kg for a duration of 6 months.

[Slide]

The results of the phase II supportive study are presented here graphically where the mean antigenic and functional activities in serum at trough levels were collected on a weekly basis over a 6-month period. As you can see, once study state was achieved, the trough levels remained significantly above the 11 microM level, as indicated by the red line.

It should be noted that the product was well tolerated during the course of both studies. In addition, it should also be noted that the mean antigenic and functional levels had a very close correspondence and this was, in fact, design criteria for Centeon's product.

[Slide]

The results of these studies clearly supported our strategy of seeking approval based upon achieving a biochemical efficacy endpoint where Centeon's product maintained trough serum A-1 PI levels in excess of 11 microM.

This strategy was initially discussed with the FDA at a pre-IND meeting in 1995. Centeon met with the Agency in April of 1997 and gained concurrence regarding the strategy and the pivotal clinical trial designs. Protocols for the 2 pivotal studies that I will discuss in a moment were submitted in February of this year. In March of this

year, Centeon met with the FDA to reconfirm this strategy. The results of that meeting led to the postponement of these pivotal studies pending the outcome of this BPAC meeting and final commitment of the Agency.

[Slide]

I would now like to briefly describe the planned pivotal studies. The first planned study is a single-dose, crossover trial comparing Centeon's product to the currently licensed product at a dose of 60 mg/kg. The primary endpoint in this study is a comparison of the functional serum levels using area under the curve. The secondary endpoint will assess additional pharmacokinetic properties.

[Slide]

The second planned pivotal study we are prepared to initiate is a phase II/III study. The primary endpoint for this study is steady-state serum A-1 PI levels, and that they are maintained above the 11 microM level with no apparent downward trend in response. The criteria for success for this particular endpoint were developed in cooperation with the FDA.

In addition, a secondary endpoint to be examined involves measurement of A-1 PI levels in the epithelial lining fluid of the lung.

[Slide]

In order to facilitate our development program,

and in preparation for this meeting, we sought additional expert advice. We asked the Alpha One Foundation to convene a group of U.S. clinical experts for consultation regarding our current program and alternative development strategies. These experts in total are responsible for over half of the enrollment in the NIH-sponsored registry discussed here today.

[Slide]

The following is a summary of the expert advice that we received. As you heard today, the top priority is to get additional A-1 PI to patients as quickly as possible. In addition, these experts felt that the 60 mg/kg weekly IV dose conveyed clinical benefit and should be approved. The proposed Centeon IV program was felt to be appropriate for approval, and to be the fastest route to approval. In fact, they felt that these studies should be initiated as soon as possible.

[Slide]

With regard to future directions, the clinical experts felt that while collection of clinical efficacy and dose-ranging data would be desirable, it should not be allowed to delay the availability of Centeon's A-1 PI product to patients.

We did have an opportunity to discuss the fact that an inhaled A-1 PI product may provide a better

opportunity than the IV product for optimizing A-1 PI augmentation therapy.

[Slide]

Indeed, Centeon is involved in a collaboration with Inhaled Therapeutics, Inc. to develop a respiratory administration system for our product. Potential advantages of an inhaled A-1 PI relative to the IV therapy include increased dosing efficiency, that is, increased efficiency of A-1 PI delivery to the target tissue, the lung, which would potentially reduce the required dose and allow for treatment of more patients. In addition, clinical trials for this technology would potentially divert less product from the patient care.

It is expected that this technology will allow for self-administration, resulting in enhanced patient convenience, comfort and compliance, and allow additionally for daily dosing which may render more stable anti-inflammatory effect. Reduced treatment associated expenses may also be anticipated.

[Slide]

In summary, Centeon's A-1 PI is a highly purified product that has been shown to incorporate enhanced purity, viral reduction, to be well tolerated in the clinical trials. It has been shown to maintain serum levels well above the presumed protective threshold of 11 microM.

We feel that there is an urgent need to provide additional A-1 PI to patients as quickly as possible, and that long-term clinical trials to fully characterize the impact of IV therapy on disease progression would significantly delay public availability of A-1 PI.

[Slide]

In conclusion, the available clinical information and the experts' advice that we have sought support the design of our clinical trials including the use of biochemical efficacy as an endpoint. Centeon is prepared to initiate this pivotal program once FDA reconfirms their prior concurrence, and we look forward to working with the Agency to realistically address the immediate and long-term needs of the patient community. Thank you.

DR. HOLLINGER: Thank you very much. The final presentation is by Alpha One Pharmaceuticals.

Alpha One Pharmaceuticals

MR. LEZDEY: Good morning.

[Slide]

My name is Darren Lezdey. I am the vice president of clinical development for Alpha One Pharmaceuticals. Basically, our corporate mission is to produce a safer, limitless supply of recombinant alpha-1 antitrypsin. Really, our objective here at this meeting is to let everybody know that there is an alternative on the horizon.

[Slide]

Basically, this is a great illustration of what we are all about. Using a proprietary insertion system, we have placed alpha-1 in yeast, put in the fermentor, allowed to multiply, to grow. We purify it, aerosolize it and deliver it right to the lung, exactly where it is needed.

This, in my opinion, is probably the most impactful slide that you will see today. So, please, everybody give at least a careful eye to it. This illustrates the rise in the diagnoses of alpha-1 antitrypsin deficiency up until the year 2002. By the way, these figures come from the World Health Organization. I think the most dramatic part of this, other than the number, is if you look down here, these colored blocks represent plasma companies. If all the existing plasma companies were to come on line with the drug -- and we hope they do, there are a lot of people who need this -- we still have this deficit to fill. I mean, even in earlier years there is still this much to fill.

So, what do we do about that? You know, what do we tell those patients? "I'm sorry, we're all out?" I don't think so. The most obvious alternative, we feel, is recombinant technology. We can produce an unlimited supply of a much safer product because, again, we are doing it through yeast.

[Slide]

Very quickly, this is Alpha One's production scheme. We start with a master seed stock which ensures the fact that we can get generation after generation the exact same product. We go to a working stock. We ferment it. We purify it using a proprietary system. We sterilize it, and then we have our bulk product which is 99.5% pure, free of human pathogens, no virus, no prions, nothing but AAT.

[Slide]

What are the characteristics of the yeast derived versus the plasma derived? Well, on a molecular weight basis they are pretty much the same. From a glycosylation standpoint there is a difference. In the human product there is about 96 hours half-life in the body. In the recombinant product it is about 16 hours, but through aerosolization that is really not going to be a problem. That is something that my colleague, Dr. Wachter, is going to discuss in just a minute.

Finally, the other components -- as I said before, there is nothing except pure AAT in our recombinant, whereas the human has various proteins, including ACT and albumin.

That is it for me. I would like to turn the mike over to Dr. Allan Wachter. We are going to share on this today. So, thank you.

DR. WACHTER: Thank you, Darren.

[Slide]

Here I would like to quote some of the work that was done by Dr. Crystal. You note, this is 1989, almost ten years ago, and here Dr. Crystal showed that with the recombinant alpha-1 made by yeast -- he was able to show that you can adequately augment patients' alpha-1 levels and neutralize the elastase loads.

Furthermore, he was able to show that in the null phenotype patients where there were no serum levels the alpha-1 recombinant transgressed the membrane and was found in serum. So, it does get into the interstitium. Furthermore, Dr. Crystal showed that these patients had no sensitization to the yeast product and it was safe.

Further work was done by Dr. Crystal showing that aerosolization therapy was efficacy and normalized. Work by Dr. McElvaney, in 1991, showed that aerosolized Prolastin for CF was able to return the levels of elastase to normal. Dr. Berger showed that you can have a dose-dependent level decrease in elastase. And, these are patients who have 550 times the level of elastase compared to 20 times the normal level in the AAT patients. As recently as 1997, Vogelmeir showed that aerosolized AAT in normal volunteers was safe, effective and convenient.

[Slide]

We are proposing that using the inhalation method you can

get similar decreases in elastase levels.

What I would like to focus in on most importantly is safety. When you are looking at the plasma product you have significant risks. What I would like to do is just tell you a little bit of the risks that I have and what I have to tell patients. When a patient comes to our office and, unfortunately, gets diagnosed we have to tell them, "well, unfortunately you have this disease, and it is a disease that has a bad outcome." But we say, "wait, we have a product available for you." And they say, "oh, great." Then we say, "well, first you have to get vaccinated." They say, "against what?" "Hepatitis." "Is there any other concerns?" "Well, there's parvovirus." And, he says, "Is there a vaccine against that?" "No." They ask, "is there any other concerns?" I say, "well, there's been product recalls." And, they say, "to what?" "I say Jakob Creutzfeldt." They say, "what's that?" I say, "that's mad cow disease." "Oh, boy! anything else?" I say, "well, there's a pinch involved. You have to get infused, and you have to go either to a doctor's office or, hopefully, you can get it at home." "Is there anything else?" I say, "yeah, there's another pinch, the cost."

Does anyone here know the actual cost? Between $25,000 and $60,000 a year. In today's market with HMOs that is very hard to convince, especially if we don't have

strong clinical data.

Then finally, after I convince the patient to take it, they say, "is there anything else?" I say, "yes, I don't have any for you." That is why we are interested in the recombinant technology. It is safe. No risk of viral or prions. It is transgenic technology that is very interesting, but there is still the theoretical risk of prion. It is cost effective. By giving it by inhalation we can cut the cost significantly, significantly -- 200 malignant as opposed to grams and grams and grams.

Quoting Dr. Pierce's lecture earlier this morning, giving it inhalationally, if patients are under stress -- viral infection, bacterial infection, you can increase it like in asthma you can give increased steroid doses. You can't do that with the present product. So, inhalation has another added advantage.

If there is an unlimited supply we can help to drive the cost down. I think that is very important in today's market, and this is something we want to do. Of course, it is patient friendly.

Some further advantages, the yeast is fully active. It does not require a heating step to inactivate human pathogens. There have been studies that show that if Prolastin is heat inactivated for 10 hours there are confirmational changes, decreasing its bioavailability.

That will not happen with a recombinant product. We don't have those pathogens to be concerned about.

Glycosylation? Yes, it is not glycosylated but by being inhaled and giving it where you have to give it, and giving it on a daily basis you can maintain normal elastase loads. Thank you for your time.

DR. HOLLINGER: Thank you. Is there anyone else that wants to make any comments of any sort from the public hearing session? Not seeing anybody, we have asked Dr. D'Agostino, from Boston, to give us a statistical perspective on several of the studies that have been presented.

Statistical Perspective

DR. D'AGOSTINO: Basically, what we have is a surrogate endpoint that just doesn't have the tie-in with later development of disease, the mortality and the degeneration of the FEV-1. So, we are in a situation where we don't have clinical trials to support the relationship and the series of studies that we have looked at really all have that common theme, what is the ultimate impact on the FEV-1.

I don't want to get into the discussion that the Committee is going to get into momentarily, but I think that one possible outcome of that is that we need to go on to randomized controlled trials, and the discussion I would

like to have in the next ten minutes or so is what are the issues that we are going to have to raise if we suggest randomized controlled trials?

[Slide]

Don't look at anything but the very top piece right now. Basically, what we have is that if we think of FEV-1 as a useful measure, what we really want to do is have two groups of individuals, those treated and those not treated, and on each individual we are going to look at what happens to the FEV-1 over time, and we are going to get a slope from them. That has been the suggested notion.

Well, what you are going to have is that in the untreated you are going to have a number of different slopes, and you are going to have a distribution of them. Then you are going to have in the treated a number of different slopes. Basically, what you are going to have is an average slope for the untreated and an average slope for the treated, and each of these distributions is going to have a variability around it. Mark earlier labeled that sigma.

What is going to have to be in our considerations is how do we get a study together that is going to have enough power to it, enough sample size so that we can really distinguish if mu1 is different than mu2, if the average slope change in the untreated is different than the treated?

Basically, it is the so-called effect size. That is what is going to drive it. How do we make sure that we have enough observations where there is going to be a real effect size that we are able to detect this difference?

I did some calculations that talk about a power of 90%. I did a 2-sided test of alpha 0.05, a formula that looks similar to what Mark gave earlier but basically it is dealing with a 2-sided test. If you take my numbers and reduce them by 20% you get his numbers. But this is what we are up against. We have outcome measures, change in slope. We want to talk about how many observations we need so that we have an adequate sample size to detect differences if they are there. We are going to worry about the differences in the means and we are going to worry about the variability.

Well, what happens in some of the discussions that Mark gave is if we increase the number of FEV-1 measures per year, and if we take the trial out to a large number of years we can keep decreasing that sigma. So, the types of things that he was talking about really related to how do you reduce the sigma, how do you get a sample size that is going to work so that basically your sigma is small?

[Slide]

Here are the years of follow-up. Dealing with the data between 35-70%, if you look at the material that was

supplied by Mark, these are what the sigmas are going to be. What I would like you to look at is that after a while, extending the study out by a number of years isn't going to increase very much. Also, in this column, here, this is if you went from 2 measures per year of the FEV-1 to 4 measures per year and, in terms of effect, the effect of 0.2 is usually considered a small effect in statistical analysis, and look at what happens.

[Slide]

If you look at this sheet, which is a much more informative sheet, this is the plot of sample size. This is the sample size needed and here are the years of follow-up. What I want to point out here is that if we took the sample and said how many years do we need, the first thing we notice is that whether we have 2 measures per year or 4 measures per year, you have to take the study out to about 2.5 years, 3 years before you get to the point where you are really going to have a manageable sample size. That is about 400 or 500 observations and we go down to about 350 there, but you have thousands of observations needed if you are in this 2.5 years.

So, the first thing that we are going to have to face is that if we use the FEV-1, and this is between 35-79% at baseline, we are going to have to say that the study is going to have to run a few years. Also, it isn't going to

be a heck of a lot of gain by taking multiple measures. This has been mentioned a number of times. The first line is 2 measures per year. The second line is taking it to 4 measures per year. So, the first thing we are going to have to keep in mind is if we really think FEV-1 and a change in that is important, we are going to have to talk about long studies, and we are going to have to talk about not really gaining a heck of a lot by multiple measurements.

[Slide]

The next thing that is probably of more interest to us and myself as a statistician is that maybe what we can do is shift from the 35-79% to other groups. If you look at the data that Mark presented, if you look at the 30-65 group, you actually go from what he was using as delta of 18% to delta of something like 30%. If you take a different group, and maybe one of the considerations we should have is that maybe we shouldn't be looking at all FEV-1s under 79, but maybe what we should do is be focusing on a group where we think the action is and they have that trough that you saw on the earlier plots. Then what you get as you start moving out is sample sizes actually decreasing quite a bit.

[Slide]

Here is what we had a moment ago. That was the sample sizes required by the 35-79. If we shift and say that, well, maybe we shouldn't be looking at all of the

ranges but we should be looking at the range 30-65, then we get the test with the same alpha, the same power and much smaller samples sizes. If we can find something with a reduction between the difference the treated and non-treated that is really dramatic, like a 50% difference, the sample sizes are actually in the hundreds, and low hundreds. This is about 79 or so. So, it is possible that we might be able, in terms of recommending a clinical trial, to have a reasonable clinical trial that has FEV-1 as an outcome, but we might want to talk about the appropriate length of time and talk about the appropriate initial amount of FEV-1 that we are dealing with. This comes from Mark's data with 30-65.

The other thing is that there has been a lot of talk about the CT. This line is basically the line that you would get if the data that has been presented on the CT. If you started off with a group that needed this many observations using the FEV-1 and there is basically a 2-, 3-fold improvement in precision with the CT, the sample size needed would drop down to this if we thought the CT was established. I am concerned about whether or not it is established. But the point that is being made here is that if we are clever on the group we select to investigate, if we are clever on the outcome variable we look at, studies are feasible; studies are possible if the data we have been

presented is in fact correct and usable for designing studies, and there is no reason to think it isn't. And, studies of a couple of years, three years duration with FEV-1 for a reasonable group, 30-65, maybe CTs as the outcome are reasonable to do.

I just want to make one last comment about the mortality. Some of the mortality figures in terms of sample sizes look quite good, but mortality is a very elusive game in terms of playing that after you have finished with the mortality study then you wonder did you die of the right thing and you start getting people saying that cholesterol forces people to commit suicide, and you may get the same thing here. You have to be careful what you mean when you say mortality as the outcome and now you are going to really believe it. Also, there is an awful lot of variability and I think the number that Mark showed you -- you would possibly need 5000 observations instead of 50 observations because of the variability inherent. I am suggesting that we stick to things like the FEV-1 change, look at the CT very seriously and studies running 2.5 to 5 years seem to have very reasonable possibilities, and those are my comments.

DR. HOLLINGER: Thank you very much. We are going to go into the open committee discussion section of the meeting today. Dr. D'Agostino is going to be sitting on the

Committee in place of Joel Verter who is not able to be here today and Dr. Moye. There are two other people, Dr. Stoller and Dr. Chamberland who are also going to join us. It looks like there isn't much room at the table but they are non-voting members. We will have the FDA representative give us a perspective and presentation of the questions. Dr. Pierce?

FDA Perspective and Presentation of the Questions

DR. PIERCE: After Dr. Campbell's presentation I thought that there might be a little bit of confusion about what the Turino article had said, that came out a couple of years ago, on the risk in SZ patients. So, I had copies given to the Committee of the paper and I would just like to read the full quote from the end of the abstract:

These observations indicate that in smokers the PI SZ phenotype confers a significant risk of the development of chronic obstructive pulmonary disease, COPD, of itself except in rare instances in non-smoking individuals. The SZ phenotype may confer little or no added risk to developing COPD.

[Slide]

The problem in looking at non-smokers is that in people who are discovered to have emphysema and alpha-1 PI deficiency, 80% or more of them have already been current or ex-smokers by the time you make the diagnosis. So, you

don't have an opportunity to ever change somebody from being a former smoker.

This is, again, from the NHBLI screening population, and Dr. Crystal mentioned about ascertainment bias. You can see that symptomatic ascertainment was present for 50% of the SZ subjects, who numbered 50, but if the members will look at Table 1 on page 3 of the article, they will see that although 50% were ascertained because of attendance at a chest clinic, the other 50% were ascertained through family screening studies. In the entire group 85% had a history of lung disease among the SZ patients. If you subtract the 50% that were known to be symptomatic, you are left with 85% minus 50% or 35% among the remaining 50% of patients, and that translates into at least 70% of those that were ascertained through family screening of the SZ patients had a history of lung disease and at least 30% of them, one would calculate ha a history of COPD.

This slide is also illustrative because it shows that the reason that the 10 patients in the registry who may or may not have been treated with alpha-1 PI, who had the SZ phenotype, didn't have that much evidence of lung disease because they were younger. They were about 10 years younger on average with a level below 11 microM compared to those above 11 microM. Again, note that in this group half of them were ascertained through family screening. The mean

percent predicted FEV-1 was distinctly abnormal at 62, going down as low as 13, and the diffusion capacity, another indicator of emphysema, was distinctly abnormal at 62, going down to 18.

Now, there is no argument that those patients who were identified and treated for alpha-1 PI deficiency are the ZZ phenotype, but clinicians are also influenced by defining the disease of severe deficiency as the cut point of 11 microM which we have seen excludes anywhere from 80-95% of SZ subjects right off the bat, and there are SZ patients who have emphysema and do receive augmentation therapy as well as other experimental therapies to try to boost their alpha-1 PI levels.

[Slide]

So, in Dr. Campbell's abstract it is mentioned that the MZ heterozygote's parents or sufficient of severely deficient ZZ patients appear themselves to be at significantly increased risk of COPD. Well, if I were a ZZ patient would I want to boost my levels to levels that were not able to keep my parents, who were just heterozygotes, from getting chronic obstruction pulmonary disease? It is a question we should ask ourselves.

Another factor, as has been mentioned, is that alpha-1 PI has a multitude of effects that have been demonstrated on markers of inflammation, that it has anti-

inflammatory properties. Now, inhaled corticosteroids, also as was mentioned by Dr. Stockley, may have an influence on the natural history of COPD but the analyses of the registry study did not include a control for concomitant inhaled corticosteroids whose use is variable here, in the U.S.

[Slide]

If we again review some of the problems with the registry study -- as has been mentioned, of course, we can't draw the same kind of inferences that we could from a randomized trial since this is an epidemiologic study, but I would like to mention that the deaths correlated strongly with education. So, if you didn't finish high school you were three times as likely to die during the 5-year follow-up as if you had at least some college.

Treated and non-treated groups were imbalanced and non-comparable with respect to baseline FEV-1, education and socioeconomic status. Now, the willingness and ability of the patient to undergo the therapy could correlate with health outcomes potentially, including death, and the American Thoracic Society noted, in 1989, that the willingness and ability to undergo therapy are among the criteria clinicians should consider whether or not to recommend therapy for their alpha-1 PI deficient patients.

[Slide]

It also is important to note that in terms of

cause of death the documentation was able to be reviewed for only a little more than half of patients, and the COPD-related deaths were not statistically significantly increased with treatment although the trend was in the right direction.

Now, the only FEV-1 stratum in which deaths were significantly less with alpha-1 PI treatment was the group FEV-1 baseline 35-49%. That group is about a fifth or about 200 patients in the trial, and 18% of all deaths. So, a group that comprised 18% of all deaths was where all the money was in terms of the apparent effect on mortality. For the other 78% of deaths, which occurred in people whose baseline FEV-1 was less than 35%, the odds ratio was non-significant at 0.83 with a p value of 0.44.

[Slide]

So, back in '96 a group of experts was convened in Geneva on alpha-1 PI deficiency, and they concluded that there was an urgent need for randomized clinical trials to assess the efficacy, and they hoped that the information from the registry study at NIH would indicate a need for fewer subjects, and I believe that we have seen that seems to be the case.

Other needs that were identified at that meeting include the need for a placebo-controlled outcome-driven trial; a determination of the need for adjusting the dose

during exacerbations of COPD; and determining the minimum optimally effective replacement dose.

[Slide]

FDA has used the CT variance data of Dr. Dirksen that you saw presented today, and we have calculated power and number of subjects needed to do basically two trials. One, a trial lasting only a year and another, a trial lasting only 18 months. Here, we have used a delta of 30% which is approximately what was seen for that 35-40 percent of predicted baseline group in the registry study in terms of magnitude point estimate of treatment effect. And, we see that for FEV-1 using a 2-sided alpha test, rather than the 1-sided alpha test that Dr. Schluchter presented, with 80% power we would need 105 subjects per treatment arm using FEV-1 as an endpoint, and for CT significantly less, only 65 subjects per treatment arm for just a 1-year study.

If we got a 50% treatment effect with CT, we would only need 24 patients per group for 1 year. With an 18-month study the numbers are for FEV-1 71 patients per group and for FEV-1, assuming a 30% change and with CT 43 per group, again, if we were lucky enough to get a 50% difference in CT in the rate of progression, we would see a significant difference statistically with only 16 patients per group, according to those estimates.

I will remind you that these were based on the

variances of Dr. Dirksen's Danish and Dutch study, and the FEV-1 entry window there was I believe from 35-70%.

[Slide]

So, as we consider various potential outcome variables for clinical studies, we could categorize them into three categories: clinical outcomes such as rate of change of FEV-1, survival, high resolution CT and counting the number of infections and hospitalizations. We could look at markers of lung destruction which have been alluded to earlier, including also marker of lung inflammation. And, I think it may be important to look at complexes of neutrophil elastase as well as free neutrophil elastase, particularly when we do bronchoalveolar lavage studies. Thank you.

DR. HOLLINGER: Thank you. Shall we have the questions presented?

FDA Questions Presented to the Advisory Committee

DR. PIERCE: I will just run through all of the questions so you can be thinking about them.

[Slide]

The first question, should FDA continue to accept that maintenance of a plasma level of 11 microM alpha-1 PI, in conjunction with demonstration of an appropriately defined increment in epithelial lining fluid alpha-1 PI elastase-related analyte levels, is sufficient for

demonstrating clinical efficacy of IV administered alpha-1 PI products in pivotal phase III studies?

[Slide]

Question two relates to if maintenance of the 11 microM alpha-1 PI in conjunction with ELF measurements is no longer deemed a sufficient demonstration of efficacy for IF alpha-1 PI products, what alternative plasma level or clinical endpoints do Committee members recommend be used to demonstrate efficacy? Examples might include mortality, serial CT, decline in FEV-1, or changes in diffusion capacity.

[Slide]

The third question is what biochemical and clinical endpoints do Committee members recommend to demonstrate efficacy of alpha-1 PI products delivered to lungs by aerosol inhalation?

[Slide]

Question four, what are the designs of an appropriate pivotal phase III clinical trial to demonstrate substantial evidence of efficacy and safety of alpha-1 administered by either IV or aerosol route?

Examples of design would be placebo-controlled, dose-level-controlled where patients are randomized to receive perhaps a standard dose and other doses, either higher or lower, than what is currently in use, active-

controlled using licensed product, or uncontrolled or historically controlled studies.

[Slide]

Question five relates to for alpha-1 PI products which are already under study, and you have heard about two today, one from Alpha Therapeutics and one from Centeon, that are already studied in active phase II or phase III clinical trials, should FDA require modification of pivotal study protocols to address the Committee's recommendations in the earlier questions? If not, should FDA require that product sponsors address these recommendations in phase IV post-marketing studies?

I should mention though about the word require, FDA has no legal authority to require a company whose product we have approved to perform a phase IV test unless the product was approved under the accelerated approval regulations, which require that not only the treatment be for a disease which is serious and life-threatening but also that the product offer a significant advantage over other available therapy. Thank you.

Committee Discussion and Recommendations

DR. HOLLINGER: Thank you. Let's put the first question up, please, and we will open this up for discussion by the Committee. Who wants to begin? The issue in the first question, of course, is should they accept that

maintenance of the plasma level of 11 microM of the alpha-1 PI in conjunction with demonstration of appropriately defined increment in the ELF alpha-1 PI or neutrophil elastase-related analyte levels, is sufficient for demonstrating clinical efficacy of IV administered products in pivotal studies? Yes, Dr. Boyle?

DR. BOYLE: Let me try to begin the questions all overlap each other.

DR. HOLLINGER: Yes.

DR. BOYLE: There doesn't seem to be agreement, and I may be wrong, from reading this that either FEV-1, given variability, or even as the last speaker said, mortality given variability in the way it is coded may be an appropriate endpoint.

But let's use mortality because dead is dead although you may not know why. If I understood the very excellent presentation of Dr. Schluchter on the various rates and sizes of samples, on mortality in order to detect a 30% reduction in mortality, and 30% reduction in mortality for a population with a high level of mortality seemed to me to be an appropriate level for approval, would require 518 per arm in a group for a total of 1000 cases over a 3- to 5-year period.

Now, the first thing, this puts it in perspective because there are only 4000 diagnosed cases in the United

States and 3000 of them or 2500 are already on Prolastin. So, either we take the people who aren't on, who are probably going to be different, or we get some of the people off to run them through this model.

Now, assuming we do this, in one of the arms, based upon the registry, there is going to be a 79% reduction in mortality because they are being treated. So, the question becomes how many people in the other arm die because they are now off of treatment in order to confirm findings from the registry, apparently from the English version, over 3 or 5 years?

Taking that all into account, it seems to me like we are trying to develop a relatively elegant way to demonstrate something that we already have evidence that there is a protective effect, and in the process of doing that, number one, we are going to have people who will sicken and die as a result of being moved to the non-treatment arm and, number two, given the fact that we know there is a shortage, there are going to be lots of other people who are not going to get access because of the delay in the clinical trials.

So, for those reasons, just to start and I will shut up now and let somebody else speak, you know, I don't know why we are changing the rules at this stage of the process. And, it is my understanding that the other

biological products that are regulated by this branch of FDA, and that would include, you know, IVIG and Factor VIII, that are not put thorough this process.

DR. MARTONE: This may have been answered and I may not have picked it up, but for the registry do we know the smoking history of the patients, and do we have any reason to suspect that individuals not being treated have a higher frequency of smoking than those being treated?

DR. HOLLINGER: Is there anyone who can answer that question for Dr. Martone about the smoking history in the study which is to be published soon, but the data was presented here from the registry? Anybody know that? Yes?

DR. CRYSTAL: I don't know exactly what the number is. Perhaps Mark remembers it. But the large majority of people who are symptomatic are smokers or ex-smokers. So I would think there probably is pretty good correlation with a history of smoking. Probably of all the variables that are out there possibly modulating susceptibility of developing emphysema with having alpha-1 antitrypsin deficiency, smoking, without question, is the predominant factor.

MR. DUBIN: Well, just a couple of short things because I think John said it pretty well and I don't want to be repetitive. I think arguably looking at immune globulins where product is being used in a number of ways with no efficacy studies and nobody is talking about fundamental

changes on that product or pulling back from people getting use. In the original Factor VIII studies, going all the way back, there were serious problems with the safety and what was reported to the FDA but the product wasn't pulled and the rules of the game changed to square that up even though later we did have some serious problems, as you all know.

I have a real problem looking at this, at this stage, and saying we are going to go back now and do these studies but we are going to go back and do them in a way that is going to cost some people some very serious impact.

The other question I have, and I might shoot myself in the foot for saying something like this, but for the first time the marketplace has actually really begun to work for hemophilia in a long time in terms of choice and product availability between manufacturer and home care industry, and I have to say our patients are very happy about that. They are very happy to have the choice of service, to have the choice of product.

Here is a population that has to depend on a single corporation with absolutely no choice, and there are two other companies that are prepared to enter the marketplace, at varying degrees of that preparation, and going back would set that back significantly and leave this population still at the behest of one company in terms or supply. So, it seems to me that if you add that issue with

the people not getting product issue, we are going to change the rules of the game in a way that is going to seriously impact this population. It is hard for me to support it looking at it from that angle. And, I think John said the other points well enough that I don't need to restated them but I would certainly ditto what John said.

DR. HOLLINGER: Bill, in answer to your question, in the baseline characteristics of that study, among those that were never on therapy 50% were never smokers or ex-smokers. In the partially on or always on group, it ranged from 11-15% for the never smokers. So, it is 11% for the never smoked in the partially on therapy or always on therapy versus 40% in the never treated. In the ex-smokers it was 50% versus 83% or 73%. So that presumably could have been taken into account during the analysis, but at least those are the baseline characteristics only.

DR. MOYE: It is my view that as scientists we must be very sensitive to our own susceptibility to pathophysiologic theories which have yet to be adequately tested. These theories are very intricate. They have longevity. They do have momentum. They are detailed. They generate great excitement among physicians and scientists. But I think that they are seductive unless we can back them up with data that demonstrates clinical benefit.

Any future recommendation, in my view, this

Committee makes, any future recommendation for approval of use of augmentation therapy must be based on -- must be planted in the good ground of authoritative data demonstrating clinical benefit. And, I think today our task is to prepare that ground. I don't think the ground is adequately prepared with the data we have seen so far. The data doesn't quite hit the nail on the head. The registry data, from my point of view, is somewhat suggestive of benefit but is also incoherent, and by incoherent I mean that I don't see the finding I expect to see for changes in FEV-1 over time uniformly in the registry set.

Unfortunately, it is also my view that further scholarly evaluations of this data set are not going to conclusively forge the link between augmentation therapy and clinical benefit. The only way that is going to be completed is if we do a prospectively designed, randomized, placebo-controlled clinical trial with clinical endpoints.

The sample size information I have seen today I think is fairly salutary. A clinical trial is feasible and is executable. There is no question that it will be painful. It will take a tremendous amount of resources to do. Pivotal clinical trials often are. Nevertheless, upon completion, I think finally, at long last after 35 years, we will have constructed an objective, relatively bias-free platform from which to view the relationship between

augmentation therapy and clinical endpoints.

DR. HOLLINGER: Thank you. Dr. D'Agostino?

DR. D'AGOSTINO: I want to make a couple of comments. The reason that one would worry about a surrogate endpoint is because you don't have substantial data that relates it to the outcome that you would really like to measure, and I am not sure from the discussions today that we have that relationship.

The other thing that I want to raise here is that in the sample size computations that Mark and I were doing we were imposing a random component. In the later computations that the FDA did, presumably there was no random component involved. I think that we probably need to have a discussion before we answer this in terms of what are the implications because I think that the short-term trials are not necessarily consistent with the registry data. You know, part of the group here may be thinking that if we say no to this we can go quickly to a few month-trial and resolve the question. I am not sure that that is really consistent with some of the data. Mark, do you want to make a comment on the sample size computation that you did and which I think was appropriate to do?

DR. SCHLUCHTER: As you saw, the slide I gave showed the variability estimates, and they were pretty stable regardless of which stratum of FEV-1 we looked at.

So, I guess I was a little bit skeptical also of the very small Ns that appeared to be required that Dr. Pierce presented.

The question also that comes up in doing these calculations is how stable were the estimates you are basing the calculations on? In a small sample you might get an underestimate of the standard deviation that could lead to an underestimate of the sample size, for example.

DR. HOLLINGER: Dr. Lauchenbauh?

DR. LAUCHENBAUH: I did those calculations and, it is correct, I did not put in a random component. In addition, these were done with an 80% rather than a 90% power.

DR. STRONCEK: I agree that a phase III placebo-controlled trial would be critical in this field. However, I think it would be very expensive, and if we require manufacturers to do that they are not going to have the resources to do it, and the effect is going to be that the product is not going to be available.

It would be helpful if the NHLBI could fund such a study but since it sounds like these recommendations were around for the last couple of years, I am not sure that they are. I guess I would like to see if it is possible -- it seems inconsistent but if it is possible to try and continue to license the intravenous product based on the current

criteria and have the NHLBI still move on to a phase III placebo-controlled trial.

I think that would get into the other questions about the inhalation products. There is no way to correlate that with plasma levels and they may have to try randomized trials using more clinical endpoints.

DR. HOLLINGER: Again, I would like us to deal right now with just the science and we can discuss cost and things like that -- I think those are important issues but let's talk about the science. What should be done; what is the best thing to be done; and then go from there. Dr. McCurdy?

DR. MCCURDY: Several things have struck me in preparing for this meeting and listening today, and I would like to build on some of the things that Dr. Moye said. The difficulties in demonstrating a real benefit from therapy, and even from demonstrating a very clear susceptibility without smoking, raised the question in my mind, a very serious question of what are we missing. Is there something else either genetic or environmental that we are missing? By focusing so sharply on what we have been doing in this deficiency, are we missing something that would be much more beneficial later on?

Not withstanding the fact that a placebo-controlled trial would be the gold standard, I don't think

that such a trial would be possible to do in the United States. I think there are too many people who believe in therapy and too few people who would be willing to either randomize their patients or be randomized. So, I don't think that it would be possible to do such a study in the United States.

That, essentially, leaves a comparison study or perhaps a dose variation study. I noticed that each of the attempts to change the dosage has either kept the infusion interval the same or lengthened it and increased the individual dose. Some years ago, I believe it was demonstrated in patients with hemophilia that if you move the dosage closer together and did them more frequently you got better plasma levels with less product. The problem, of course, is that you may run out of veins more rapidly when you do it that way. But I think that maybe increasing the frequency and decreasing the dose might give you a slightly different approach to it. But I think probably dose variability studies or comparative with current product is about all you can do in the present environment.

Finally, I have a scientific question that I have not heard discussed, perhaps not totally pertinent, but if this is as common as it is, what is the heterozygote advantage? For any polymorphism to get this frequent, there almost has to be an advantage to the heterozygote that

allows it to come up to this level.

DR. HOLLINGER: Thank you, Paul. You know, we have all of this large bundle of material that came from all these studies, and I must say, I have walked away also with the feeling that, well, there may be a trend there but there were so many problems with these studies that were uncontrolled, and if they had done this back in 1987, when they should have, we wouldn't have this issue that we have right now. But now we are facing the same problem.

For example, in the NHLBI study, in the registry, when you have something like -- although you can't prove it, when you have something like 60%, 70% in the never treated group that had FEV-1s above 80% and it was 6% or 7% in the treated group, you have to worry about the data and the validity of the data. Now, it may be all right, and there may be manipulations statistically and so on, but you have to worry about these. And, that was just a major issue. There were a lot of other issues also in terms of physicians. Why did they put these patients on treatment and other groups they left off of treatment? All of these can result in a great deal of bias.

So, from my standpoint, I have walked away thinking, well, from a theoretical standpoint it seems reasonable. There is a lot of data suggesting that the 11 microM level seems to have some relevance at least in the

patient population. Whether raising it to that level has some benefit though, I am unclear from all of these studies. I just don't -- I personally do not have a feeling that the augmentation therapy has shown that kind of benefit, and I think that what is needed is a placebo-controlled trial that evaluates it.

Now, the Dutch and the Danish are the only ones so far that have this. I talked to the gentleman who presented, before Dr. Dirksen I believe it was, who said that it was an allocated group. That is, they took their registry. They selected patients who made their inclusion criteria. They asked them if they wanted to participate and then they randomly allocated them to the different groups. One group received albumin; the other group received the product and the products apparently were very close to each other so that the patients did not know which one they were receiving. That is about as close as you get, and I must say they had to work very hard to show a difference, and there was certainly a trend down with the CT studies at 0.07, but, you know, they had to work hard to get that data, and you are looking at a whole lot of data. So the question now, when you are comparing so much data is, is the 0.07 really an appropriate probability endpoint?

So, anyway, from my standpoint, I think that a study needs to be done. We have done this with the HIV

population when there has been a problem. You can set up a data monitoring group to make sure that along the way if there are really excess problems that occur you can stop the study. So, there are ways that you can design a study to do it. So, from my perspective, I think that that kind of study needs to be done. Yes, John?

DR. BOYLE: I think I am agreeing with you, but it seems to me very clear that one of the questions is the proper dosage level for what we are trying to achieve. Right now that is not going to be studied because there is not enough to go around. A phase IV study in which you are looking at dosage is an appropriate recommendation. In point of fact, it may not have the force of law but, quite frankly, the insurance companies are going to insist on looking at that type of information as people are coming in and asking for it, not the $25,000 to $50,000 but the $75,000 to $100,000 worth of product.

But if there is enough product available based on equivalency, it is entirely appropriate to start looking at dosage and seeing what the effects, which would answer some of the questions that have been presented here.

DR. D'AGOSTINO: I think the phase IV study would give you an awful lot of nice information about it, and so forth, but you do have an uncontrolled aspect of how the dose is being allocated by the particular physicians, and so

forth, and are you talking about a phase IV study that is basically a phase III study where there is really randomization, or are we talking about it being allocated as the physicians deem appropriate? You can get an awful lot of nice safety data on those type of studies, but I am not sure that we are going to be able to really get the efficacy answered. I mean, there is something assumed that the efficacy is there and we want to learn more about it, and I am afraid that we are still grappling. We don't really have the establishment of the first question of efficacy.

DR. HOLLINGER: The numbers that you had put up, those were per arm or total?

DR. D'AGOSTINO: Per arm.

DR. HOLLINGER: So when you are talking about 150, 170 we are looking at 340 --

DR. D'AGOSTINO: Yes, and one of the things I was trying to make clear there is that if we are careful about whom we select in the studies -- I mean, I don't see why you have to have everybody who has the condition be part of the study. If you are careful about whom you select, and if we go to some of the endpoints like the CT -- and I would be very careful for the reason you mentioned, that the CT pops up a couple of times but there is nothing to convince us that it really has even attained statistically significance because of the multiple testing. But if we spend some

frond-end time thinking about the particular outcomes and about the particular patient population you want to investigate, the studies don't necessarily have to be that huge. Unless there is something magic about these European studies, I think the length of time is still a question. It doesn't seem like any of the data that the registry would indicate that you could do it in a year. But even that could be looked at much more carefully, and I think it could be studied with a reasonable length with a reasonable number of patients. It could, in fact, be mounted as one study as opposed to two, that type of thing.

DR. HOLLINGER: Dr. Brantley presented this morning the issues about the very elegant study in the lung of what is going on with all these patients. Was there any information on patients who had more serious disease? I think the data was on mildly deficient individuals. I would like to maybe know if they looked at patients with more significant disease. I mean, these kind of studies might be of some benefit in a trial at least early to see whether there are some subtle changes in these very important issues.

DR. BRANTLEY: I think it is important that the Committee understands some of the technical aspects of the kind of work that we do. Obviously, I mean, I was taught by Ron Crystal how to do this sort of stuff and we always sort

of, you know, go where the money is which happens to be the lung. But there are some technical aspects to doing these kinds of studies, and one of the things is as an individual's lung function begins to deteriorate, the ability to do successful and high quality bronchoalveolar lavage goes down, and there is a higher chance of inaccuracy as far as biochemical data.

One of the reasons, obviously, that we focused on the milder group is because we felt that we could get very, very good data regarding good returns and that we weren't going to have a sampling error that sometimes you have when somebody has more severe disease.

When we were showing correlations, let me sort of point out that there was a fairly nice correlation between impairment and the burden of, for instance, some of the biochemical markers like neutrophil elastase. Again, we didn't have individuals that went down below 70% of predicted, but even in that area right there, there was clearly a correlation with greater degrees of lung function impairment with biochemical markers.

I think it would be very difficult to get accurate information in individuals, in my experience, that have FEV-1s less than 50% of predicted.

DR. HOLLINGER: Thank you very much. Dr. Linden?

DR. LINDEN: I guess I have a concern that is

really similar to the issue that came up yesterday, the concept of applying different and higher standards to new applicants versus existing products. I mean, there is a product on the market, and I guess I am troubled, in the absence of really compelling specific data that documents exactly what needs to be done, requiring additional measures.

Clearly, a randomized trial would be desirable and I think it could be looked at as a separate issue, but there clearly is a need or perceived need for additional products and I am reluctant to create impediments to that based on the data that we have seen.

DR. NELSON: You know, it is an interesting issue. I am not sure that because a product is being used that that automatically would mean that if you were going to do a clinical trial you would have to withdraw the product that is available and not continue to make it available. I think you could do a clinical trial after a product had been licensed and used. Smoking has a profound effect and the groups aren't balanced in the natural history. We just need to know how that affects the progression, and you could do that in a clinical trial. You could select people that were equivalent. If it was early enough in the natural history that you could measure early deficits, then the people that got placebo -- if the drug was useful, could still benefit

before they reached end-stage disease. So, I think a clinical trial should be done, but I don't think that means that the drug that is on the market -- that those people who are receiving the drug now can't continue to have it. But still it is important to answer the question. You know, if it is answered and we show a definite benefit and we can quantitate it, then there would be a lot of pressure to get more drug available.

DR. BOYLE: I don't know if this is even doable but one of the things that we do know is that there is almost no product available in Europe and there are lots of people who need it in Europe. Is it possible to set a different standard for export label product? That is, for anything that is being exported, that it requires the two-arm clinical trial?

DR. HOLLINGER: The FDA is nodding no, not possible.

DR. BOYLE: It would solve our problem though.

DR. NELSON: There is a precedent. There is the pertussis vaccine.

DR. HOLLINGER: Say that again, please.

DR. NELSON: There is the pertussis vaccine trial which was not possible here but was done in Scandinavia, where the question wasn't -- I mean, a U.S. trial was done in Scandinavia and the results were then applicable here. I

think it is not impossible.

DR. HOLLINGER: Yes, please?

DR. FEIGAL: David Feigal, from FDA. Just to clarify quickly, one thing that is separate is the process of licensing. If it unlicensed in some European countries they can still set different standards and requirements before they license it. Also, in Europe, as in the United States, the decision about licensing and reimbursement is sometimes separate, and sometimes the demands of those who pick up the bill ends up in doing studies. So, that is another setting. Since there is a lower use pattern in Europe there may be more opportunity; there may be more uncertainty and an opportunity to do trials here that aren't here. But in terms of the export restrictions, it is a global economy these days.

DR. HOLLINGER: Thank you. Yes, Miss Knowles?

MS. KNOWLES: Two comments. First of all, Bayer is a big company and I am actually kind of surprised they don't have their own manufacturing plant for their European operations, number one.

The second question is and, again, I am sort of new to this so bear with me, but would it be appropriate to do trials with Prolastin as the standard against some of these newer agents, much like AZT and all the newer antiretrovirals, etc., etc., combination therapies?

DR. BUCHHOLZ: I think there has been a lot of conflicting information that is very difficult to assess that has been presented this morning. It seems like there are two questions. Number one, is this therapy something that works? Number two, a question that appears to come up as to whether the dose that is currently employed is appropriate?

It seems to me the question of does it work is a valid question, but the time to address that question probably was several years ago as opposed to the present circumstances.

While I would agree that scientific studies are important, I think we also have to consider that there are many patients who are dependent upon this; that there is a shortage of product. And, I would wonder if a reasonable compromise might not be to allow manufacturers to continue to gain approval at an indication of the current dosage, but then also permit and encourage manufacturers to do dose-escalation studies so that you could provide therapy to those patients who are diagnosed and undiagnosed and also, presumably, if this is beneficial treatment, by showing dose-escalation study differences between the standard treatment group and the subsequent higher treatment group you could, in fact, address some of the issues.

I would agree that the science here is not good,

but it seems to me the time to have addressed the science in terms of good science was years ago, and today we are in a situation where I would think there are some alternatives that would allow us to make the best of a kind of bad situation.

DR. HOLLINGER: Okay. Well, let's try to vote on this first question. You all can read the question that is up there. I think the key phrasing in the first question is probably the words "is sufficient for demonstrating..." I think that is really the question that they are trying to get at in what precedes it. So, why don't you all read the question and then we will vote on it?

Okay, all those that agree with the question that the FDA should continue to accept that maintenance of this plasma level of 11 microM, with demonstration of an appropriately defined increment in epithelial lining fluid alpha-1 PI, neutrophil elastase-related analyte levels is sufficient for demonstrating clinical efficacy of intravenously administered alpha-1 products in pivotal phase III studies. All those that vote yes on that basis, please raise your hand.

[Show of hands]

All those voting no?

[Show of hands]

All those abstaining?

[One hand raised]

One. And our consumer representative?

MS. KNOWLES: I would like to abstain.

DR. HOLLINGER: And our industry representative?

DR. BUCHHOLZ: I vote yes.

DR. HOLLINGER: Could you read the vote, please, Dr. Smallwood?

DR. SMALLWOOD: The results of voting are 11 yes votes, 3 no votes, 1 abstention. The consumer representative abstained and the industry representative agreed with the yes vote.

DR. HOLLINGER: Could we have the second question, please? I don't think the second question would be applicable, would it? Yes, the second question would not be applicable based on the first vote.

DR. D'AGOSTINO: I just want to understand what we just voted on.

[Laughter]

We are saying a new product comes along, a new product not an old product that is on the market already but a new product comes along and it is all right to do something that we really think hasn't been established to tie to FEV-1, and mortality, and so forth, because an old product was approved?

DR. HOLLINGER: No, as I understand it, it was

saying that if a new product comes along and they can demonstrate those two items, that it has a trough level, I presume, of 11 and they have an increment in the epithelial lining fluid of a certain amount, that is sufficient for demonstrating clinical efficacy. That is what I basically understood what the vote was, and the Committee is essentially saying that is all you need to do, just show that you can increase it to 11 and you don't have to do anything further. Yes?

DR. MCCURDY: Another possible interpretation is that the Committee voted not to change the standard at this particular point in time, not so much because the science supported the standard but it might be disruptive and you might allow a product to stay on the market that was not efficacious --

DR. D'AGOSTINO: That is what I am trying to sort out. Is it sympathy for existing products or is it science?

DR. MCCURDY: My vote was not to change the situation at this particular point in time. I am very uncomfortable with the arbitrary 11. Some of us remember that we arbitrarily set the transfusion level for sickle cell anemia patients somewhere in the middle 30s, and I have sort of lost track of the field recently but that may or may not be so. Some of us also remember that uncontrolled trials said androgens were good for aplastic anemia, back in

the '40s, and I am not sure we have gotten rid of that one yet, completely.

DR. ELLISON: If I can just explain the way I did, I didn't hear anything better posed as an alternative, and I think that until something better comes along you should hold any new products to the same standard that you held the previous product to.

DR. HOLLINGER: Yes, Dr. Nelson? You abstained?

DR. NELSON: Yes, I abstained because I thought the 11 has not really been demonstrated to be the proper endpoint, and I didn't want to inhibit the possibility of a trial with a clinical endpoint that was meaningful on the natural history. I am not sure just maintaining a level is it. And, I think if we continue to license products without any need or concern about another endpoint, there never will be a trial. I don't want to inhibit a trial but I don't want to take the drug away that is currently being used without evidence of either efficacy or no efficacy.

DR. OHENE-FREMPONG: Well, I just wanted to add that the second part of that sentence in the question, in conjunction with demonstration of the other effects I felt strengthened to some degree the weakness of using just a level of 11. I hope that that is not lost in how these agents are evaluated, that it is not just the serum level but all the other factors that may strengthen the ability to

make some correlation with clinical outcome.

DR. HOLLINGER: Okay. Dr. Linden?

DR. LINDEN: I just want to clarify, my reasoning was basically the same as Dr. Ellison's but also just to point out that the question said "would be sufficient" not is the only thing you could do. So, if there are other endpoints that could be done, I mean, this would not, you know, stifle innovation for looking at other endpoints that might be even better. But this would be acceptable because it has been acceptable.

DR. D'AGOSTINO: I know you want to move on but, I mean, are we saying that we really think this is the science that is sufficient? I mean, you can have all sorts of sympathy for voting yes but are we saying that we really think that when you have gone through these two hoops you have really answered the question of efficacy?

DR. NELSON: I think you show that the lung is or isn't being destroyed --

DR. HOLLINGER: Use the mike, please.

DR. NELSON: You know, I think that this is not really a biological endpoint that we are showing.

DR. D'AGOSTINO: No, I realize that and it is that added piece is really what I am trying to understand.

DR. KAGAN: I think we heard some interesting comments this morning that would suggest that there may be

other endpoints that might require validation by clinicians in studies in the future, particularly if there is an aerosolized administration system. What will be those significant endpoints? So, I think once those are developed and validated in clinical non-drug specific trials, I think we will have better endpoints to benchmark our treatment methods with.

DR. HOLLINGER: Okay, thank you.

DR. MOYE: Why would those ever be developed? I mean, what is going to be the energy that leads to development of very difficult endpoints when, in fact, attaining those endpoints isn't required for approval?

DR. KAGAN: I think companies may not necessarily have an interest; I think clinicians always will. I think clinicians will be interested in looking at endpoints even though industry may not have the same interests.

DR. MOYE: Okay, and how then do we link the augmentation therapy with the endpoints? That is all we are asking for here, the objective information that finally links augmentation and the biochemical changes with the clinical parameters. And, if we don't insist on this here they are not going to give it to us.

DR. KAGAN: I can't answer that specifically.

DR. STRONCEK: My vote for yes was to make a product that looks like it is available and that patients

are dependent on. A vote to do a study now would mean that product is not available. I do believe we need science but as move down the questions, I think the aerosol therapy is a different issue. It is a therapy that is not available. The plasma levels are meaningless. I think at that point we can make some tougher requirements for scientific study before that is approved. So, I think we have the opportunity to do both things, to let products still come out on the market so we do have products available and, yet, to ask for new studies to be done in the future.

DR. HOLLINGER: Let's move on to that question, the third question, which is what biochemical and clinical endpoints do Committee members recommend to demonstrate efficacy of alpha-1 PI products delivered to the lungs by aerosol inhalation? Yes, Dr. Nelson?

DR. NELSON: I think a good endpoint was shown. I don't know too much about it but those CT scans where they showed disappearance of lung tissue, that is a morphologic, biologic hard endpoint that I think somehow should be able to be quantitated.

DR. MOYE: I did see one slide this morning that I thought demonstrated the relationship between the CT findings and the FEV-1, and that patients who had higher FEV-1s tended to have less pathology on CT findings. Are we willing to accept that information as demonstrative of the

adequacy of the CT surrogate? Unless we are, then CT is just a surrogate as well. I did see one slide. Is that the current feeling, that it is an adequate surrogate for FEV-1 change?

DR. HOLLINGER: Any other comments? Yes?

DR. OHENE-FREMPONG: Just a question for those who may be familiar with this therapy, because I am not, is there any other reason to give this drug intravenously, other than the pulmonary benefits? Is there any other reason why a patient who is deficient may want to have elevated levels, serum levels?

DR. NELSON: Liver disease.

DR. HOLLINGER: Yes, but it doesn't seem to benefit that at all, and transplantation does not seem to, I don't think so.

DR. STOLLER: I am Jamie Stoller. I am privileged to be a guest of the Committee. I wear several hats. I sit on the board of directors of the various patient groups, and I was the deputy PI of the NHLBI registry; working closely with Dr. Schluchter and Dr. Crystal.

The answer to your question is that really there would be no there rationale, no other clinical benefits for intravenous infusion. The pathophysiology of the liver disease is rather different. It is not an elastolytic change in the liver but inclusion of the unsecreted proteins

so that there would be no other clinical benefits.

I would just perhaps like to make a few remarks in regard to the conversation that has gone on. One, I think in phrasing the initial question, just returning for a moment, if I may, to question number one about clinical outcomes, those in the field make an important distinction between biochemical efficacy criteria and clinical endpoints. As a clinician, I think it is important to realize that clinicians will recognize the efficacy of this therapy, whether aerosolized or intravenous, by clinical measures. So, some of the issue is the phrasing of the initial question, I think, that is a little bit delicate with regard to existing approval versus new knowledge, as the Chairman has so eloquently stated.

I think with the issue of aerosolized therapy, there is the insistence on clinical efficacy issues, it seems to me, that clinicians will recognize as adequate outcome measures because, obviously, serum levels will not be reliable. So, I agree with this member of the Committee who articulated the difference between existing drug and new drug as a springboard, if you will, for thinking creatively perhaps outside of the existing box about the necessity of elements of evidence.

I think the other issues that have emerged today that are important are the realization that the initial

notion about the impediments for a randomized trial, namely, the rigorous number of patients required and so on, have, with newly found information, become somewhat more relaxed because I think we have heard whether one uses CT, spirometry, mortality -- and I should say with regard to mortality that we have, in fact, looked at the mortality experience in the registry and in that sample of patients for whom mortality has been reviewed by a death review committee, the cause of mortality was almost always, 75%, related to lung disease. And, that group for which mortality was examined, for which records were available, was, in fact, comparable with regard to baseline features of those groups of patients who died and for whom rigorous review of the records were not available.

So, the Committee should not labor under the impression that the mortality was related to events unrelated to the pathophysiology of alpha-1, leading me to believe that mortality is not a ridiculous outcome measure in this particular regard because the data would not be confounded by issues of cause-specific mortality being unrelated to the biochemical plausibility of the effect of drug.

So, with regard to the question on the table now, it is my view and view of the understanding we have come to that prior impediments to a randomized trial are somewhat

more relaxed now in terms of the rigors of patient numbers, and the fact that there is a patient advocacy community which is keen -- and I think you have heard John Walsh address this eloquently -- keen to learn of an effective drug and to be provided with drug that is not only available but, in fact, is effective. The Committee should certainly think hard about clinical outcome measures in a randomized trial for new therapies coming down the pike.

DR. HOLLINGER: Thank you. And these clinical endpoints would be the usual things that you just mentioned, the serial CTs, decline in FEV-1, infection rate, mortality?

DR. STOLLER: Yes, they would.

DR. HOLLINGER: Any other thoughts?

DR. STOLLER: Well, I would agree with the other member of the Committee who said that the engine to develop clinical information will not come from clinicians laboring in the vineyards, as I do, trying to sort out these clinical issues. The mechanism for pursuing understanding of the relationship between clinical outcome measures and novel outcome measures is, in fact, either NHLBI research or, in fact, partnership with the pharmaceutical world. So, I think we need to recognize that the understanding of the surrogate endpoints will, in fact, come from the same mechanism of doing the study we are talking about now.

DR. HOLLINGER: Thank you.

DR. KAGAN: My only comment is we heard some information this morning relating to the pathophysiology of the disease, and I would think that some of the biochemical endpoints would come from results of bronchoalveolar lavage in patients receiving aerosolized treatment, particularly looking at lymphocytes and other cytokines that are present.

DR. FEIGAL: I just wonder if I could make some comments. Actually, I went out here to be a member of the audience because these are less FDA comments than my own personal comments on designs.

One of the real challenges in thinking about even contemplating study mortality in a chronic therapy is that you have the opportunity to cross people over. If we look at the studies that typically rely on mortality, they are often cancer studies where you do an intervention that you do at the start of therapy and then you watch. And, you can't redo surgery; you can't redo initial irradiation. You may be able to change chemotherapy a little bit. And, you don't have the ethical dilemma then of sort of watching and seeing how it all came out.

The other setting where we have very successfully seen mortality differences is when we have all underestimated how good drugs have been. Those have been drugs which were typically demonstrated to show a difference in disease progression but were stopped by a data safety

monitoring board early because they had a dramatic effect. In the case of several AIDS therapies that even included survival benefit.

What you have to think about here is what a data safety monitoring board would have to look at to get to an endpoint, the mortality endpoint, would be to have all the information on declining FEV-1s, worsening CT scans, whatever kinds of measures of quality of life or functional status deteriorating and hanging in there and not crossing over the patients until you had a mortality effect, or having some kind of crossover and then watching and seeing that, in fact, your early versus late design translated into a mortality difference.

I think what we really need with chronic therapies is to all work on the technology of assessing the morbidity of the disease that we, as clinicians, recognize progression and the kinds of things we are trying to prevent, the kinds of things that make patients housebound or oxygen dependent or other kinds of things, and work towards those.

I think when we look at the difference between an early laboratory measure like FEV-1 and then the bottom line being mortality, those are still useful parameters because probably the clinical progression is going to be somewhere in the middle, between those two, and we need to think about how we would design that and how we would do that.

I agree with the comments, again speaking from my own personal opinion not policy, that for novel therapies and new therapies this is really where we need to demonstrate what we can tell people to expect from these treatments.

DR. HOLLINGER: I think we have probably answered that question without specifically going through that. So, I think we will move to the fourth question on here, what are the designs of an appropriate pivotal phase III clinical trial to demonstrate substantial evidence of efficacy and safety of alpha-1 PI administered by IV infusion and by aerosol inhalation?

I am not sure what the issues are or what they want with this question. It lists examples. These are all obvious examples.

DR. D'AGOSTINO: They may be asking, if we are so convinced in question one that we have efficacious products out there, maybe we should say that placebo-controlled trials are no longer appropriate. That is one possible statement we can get out of this.

DR. HOLLINGER: For IV infusion and for aerosol inhalation or just for IV infusion?

DR. D'AGOSTINO: Well, it may be for both. I don't know what they are trying to get at, but I guess that is a possible interpretation.

DR. NELSON: Well, if we were 100% sure that intravenous infusion of the drug is efficacious, then we could see if aerosol was equally efficacious. But I am not convinced that we are 100% convinced that intravenous infusion is efficacious. So, I would think that if you enrolled people early enough in the disease, newly diagnosed patients, that you still could do a placebo-controlled trial without taking the people who were on the drug, who have been receiving the drug, off the drug or making it unavailable. And, I would think it would be conceivable with an endpoint such as FEV-1 change or radiographic change in CT.

DR. HOLLINGER: Short of that, you could make the comparison, if you had to, if you didn't do a placebo-controlled, compare inhalation with the current product that is available and consider it either as an augmentation with benefit or placebo. But you wouldn't have that benefit. Yes, please?

DR. D'AGOSTINO: Jumping to the end of the list, I would hope that we would say that we didn't think historical controls were acceptable.

[Laughter]

I know I don't.

DR. HOLLINGER: Any other comments? If not, let's look at the fifth --

DR. PIERCE: May I clarify? The intent was really to ask the question separately for the IV products and for the aerosol products, and we wanted to know -- here are some examples of control groups. We would like to know for each separate case, and particularly now for the aerosol inhalation, which of these choices of control groups are acceptable? Are they all acceptable or is it only a subset?

DR. HOLLINGER: Okay, let's look at just the IV infusion. You have heard that there are some differences of opinion about placebo-controlled trials. Most feel that they are not acceptable. Some feel that they should be done. That is one thing that I think has come up already. Am I correct? Okay.

Now, the second question we have dealt with somewhat with intravenous infusion. Should there be a dose-level controlled study. That is, with a standard dose and with a higher or lower dose, and one could probably say maybe you don't need the lower dose although, again, you don't know. I didn't see that being done. Most of the studies were done with 60 mg/kg or 120 mg/kg. There were some studies done biweekly, some done monthly with 4 times the amount, 240 mg/kg on the monthly ones. We have seen some of that data.

So, the question then on the intravenous ones, do you believe -- does this group believe that one should

recommend -- the FDA has the right to do whatever they are going to do, anyway --

[Laughter]

-- I mean, after all, this is an advisory committee, and they are listening to what is being said. So, what about a dose-level controlled trial? The other one, while we are looking at them, is active controlled using licensed product. Can someone explain that to me? I am not sure. A comparative trial?

DR. PIERCE: In this case it would be against Prolastin. You have seen that in the trial by Alpha Therapeutics which is winding down. It has a positive control against Prolastin, and Centeon plans not to do that, and their comparison is a single dose PK study against Prolastin.

DR. HOLLINGER: Okay. Then the last one is uncontrolled. Do I have a sense that we should not do an uncontrolled historical control trial? Can we leave that one out? If we can, does somebody want to talk about the dose-level controlled or the active-controlled using licensed product?

DR. ELLISON: Are we still on the intravenous product?

DR. HOLLINGER: Yes, we are just talking about the intravenous infusion now.

DR. ELLISON: I think it is highly desirable but I don't know, can the FDA required that of a licensed product? I mean, it is already out.

DR. HOLLINGER: Well, let's take it generically. We will let them worry about whether they can do it or not.

DR. ELLISON: I think a dose-response study is desperately needed with, I think, both lesser as well as perhaps higher, once they get enough product available, if they can do such a thing.

DR. MOYE: I think a dose-level controlled study is fine as long as one dose is placebo.

[Laughter]

DR. HOLLINGER: We hear that. I think they have heard that. Go ahead.

DR. BOYLE: I am confused. If we recommend a dose-level controlled phase III and one of the companies that is already in phase III has an active control, does that mean we are rejecting their methodology?

DR. HOLLINGER: No, I get the impression they really want to know if we think this is a good idea, not necessarily whether they are going to require it of anybody. But, if you are going to ask for something, do you think this is a good recommendation, dose controlled.

DR. PIERCE: Could I just mention that there is another question that deals specifically with products

already under development. So, this question is more, you know, if future companies come along and want to develop an IV product, what do they need. Then you have a separate later question about the products already under development. So, you have the opportunity of splitting it if you want to.

DR. KOERPER: I haven't spoken yet but I don't think it is ethical at this stage to do a placebo-controlled study even though, yes, it would have been nice to have done it before there was product available. But now you have patients on product, and how can you deny them?

This is analogous to the placebo control with AZT, but once AZT was approved everybody gets AZT and everything is compared against AZT. The same thing for cancer studies. There are no cancer patients who are given no treatment now. They are given something and the new thing is compared against the existing. So, I think that you can't ethically do a placebo-controlled trial at this point.

I do think that using active control where you compare the new product to the previously approved product is reasonable. I believe that we need those controlled studies eventually because it may be that the reason that the present product is not showing efficacy is that the dosage is too low, or the dosing interval is too far apart. But I don't know that you can require that for a phase III, and I would hope that clinicians would want to establish

this on their own.

Lastly, there is precedent for clinicians doing studies, publishing results in reputable journals showing that a previously approved product doesn't work, or doesn't work at existing dose, and the medical community then changes their practice based on those studies. So, I don't think that we have to obligate the company to do the perfect, complete, all-inclusive study at this point. I think it is more important to get product out there and then the medical community will refine the indications and the dosages.

DR. HOLLINGER: Perhaps the AZT was not a good one because there were multiple well-controlled trials done prior to that --

DR. KOERPER: Right.

DR. HOLLINGER: Then, I agree. Once it was out, that has been the standard --

DR. KOERPER: But I don't think you can go back ten years.

DR. MOYE: But the problem is we haven't made any progression in ten years. You know, you may believe that augmentation therapy works, but we don't know that it works.

DR. KOERPER: Well, I don't know that we have the right dose. If we were to treat all hemophilia patients with 10 units/k we would say Factor VIII doesn't work to

stop bleeding because 10 units/k is too low a dose. So.

DR. MOYE: I can't speak to that. I don't know the details about that but I have read this, and there have been calls for many years from many esteemed authors for placebo-controlled trials. Active-controlled trials make very good sense if you know -- not if you believe but if you know the active control beats placebo, and we don't know that augmentation therapy beats placebo vis-a-vis clinical endpoints.

DR. KOERPER: But I don't think we know that we have the right dose. I think we need a dose escalation study to find out the right dose of this.

DR. MOYE: So, then perhaps that should be a preliminary study to identify the right dose and then, once you have identified the right dose, move to a placebo-controlled study to finally demonstrate efficacy.

DR. HOLLINGER: So, you might get your answer if you go down to 1 mg/kg --

DR. MOYE: And give a homeopathic dose, right.

DR. KOERPER: Well, it looks like this is a homeopathic dose for some people. One could argue that if we are not showing benefit, giving enough to get to 11 microM is a homeopathic dose. Then we can go up from there.

DR. LAUCHENBAUH: A couple of comments about the active control and dose level control. I think I detected

some misunderstanding about an active control trial essentially being a test of Prolastin. It would not; it would be a test of whether this product is the same or at least is not inferior to Prolastin. So, in that case you would be looking for are we not much worse than Prolastin. The dose level control study has the potential problem that if your dose levels don't show a difference you are left with not understanding whether the product is completely inefficacious, or whether it is efficacious but the dose levels are not different.

DR. HOLLINGER: Thank you. Yes, Dr. Nelson?

DR. NELSON: Going back to the AZT. I think the development of AZT was really well done, carefully, quickly done. But without the trial, you know, showing the difference in mortality etc., AZT would not have been the standard of care.

But there was another trial, the 019 trial, which started with people with CD4s over 500. It was a placebo-controlled trial, and that trial showed significant fall in CD4 count and some symptoms without mortality. After the trial in the other study showed differences in mortality, then it became the standard of care.

Well, that is kind of where we are now in a way. We could do a trial, I think, placebo-controlled -- I think that is important because we are really not sure whether

this drug works at all, and if you don't know whether it works at all then the dose is irrelevant. I mean, the dose is a secondary question, not a primary question. Therefore, I would say that a placebo-controlled study in people with early disease would give the least harm to patients in the course of their progression, with possibly the most benefit to the whole community, but continue the people who are on this licensed product, not de-license this drug. I don't think there is evidence for de-licensing it. You know?

DR. MITCHELL: I guess I disagree. I think that the weight of the evidence shows that the drug is effective. The studies aren't good studies. They are not done well. But, you know, the epidemiological study that showed that there is a difference in survival, to me, is a very weighty study. Yes, it is not a controlled study; it is just a registry that happened to show something. So, I think that there is evidence that it is effective.

I also think it would be unethical to do a controlled study because of that. I also think that the product should stay on the market and that FDA should continue to use the same type of standard.

I think that there needs to be more information but I am not sure that we should require the manufacturers to do that. I think, again, that perhaps the clinicians should be doing those kinds of studies.

DR. MOYE: But how is that going to happen? I mean, I understand the call, the plea for more information. I am sounding it too. But if we don't require the information we are not going to get it. The Institute is not going to fund a study. And, I don't know what you mean by individual doctors. I mean, how are they going to have the wherewithal to put together studies that may involve 100, 150, 200 or 250 patients? I mean, there has to be some underlying way by which that comes together and by which that is funded, and the government is not going to do it. I think the people to do it are the sponsors, and they are not going to do it unless we require them. So, we are not going to get the information that we all need unless we demand it.

DR. BUCHHOLZ: Has the question been asked of the government or of NHLBI? I haven't heard anyone say that issue had been addressed and refused.

DR. HOLLINGER: Does anyone know? Dr. McCurdy?

DR. MCCURDY: Number one, I don't know --

[Laughter]

DR. HOLLINGER: I don't know either.

DR. MCCURDY: Number two, the representative of the Lung Division that was here had to leave and catch a plane for Dallas. So, we can't ask them. Certainly, it is an issue that can be explored. I can make no promises as to what will be done because, among other things, I don't know

all of the overall priorities in the Institute. But it is an issue that can be explored. I think it is unlikely to be done unless the Institute does do it, NHLBI or some similar organization raises the funds to do it.

DR. D'AGOSTINO: The individuals who are opposed to the placebo control, are they opposed to the design that was suggested for people at an early stage? I thought that was a rather clever way of getting a placebo-controlled trial that could address the question of is the drug useful at all and still have --

DR. HOLLINGER: Early stage meaning the 35-79% group?

DR. D'AGOSTINO: Right. Are people opposed to that?

DR. HOLLINGER: I thought that was fairly -- and it is a small number, talking about 2.5, 3 years possibly, and selecting a specific group, the ones from 35% to 79% and following that group along very carefully, monitor it well and making decisions along the way. I would think that you could do it. I don't think it is that big a deal.

DR. MCCURDY: One of the problems with the Institute or any other group doing an appropriately controlled trial, either placebo-controlled or multiple dose-controlled, with the basic premise that if some is good more is better and you may be able to show a difference

there, would be whether the trial is doable; whether you can find physicians and/or patients who would be willing to be randomized to either a placebo-controlled trial or a multiple dose type of trial. It is not a given that it is a doable trial.

DR. STOLLER: Just as a point of clarification on the issue of early disease, I think the data that you saw Dr. Schluchter and Dr. D'Agostino present with regard to the subgroups in the registry where the delta was biggest is not in the early disease group. The FEV-1 of 35-49% predicted is, in fact, a moderately to severely impaired group, and the statistical requirements for a randomized trial for the "early" disease group are far more rigorous -- the numbers are far, far greater. So we shouldn't labor under the assumption that the appeal of doing at study in the early group offsets the ethical dilemma because there would be no practical opportunity to demonstrate efficacy based on the power requirements in looking at an early disease group. We are really talking about a targeted group as an efficacy outcomes of the study with stage 2, 35-49% predicted FEV-1 where 80% or above is normal. So, this is a group with fairly established emphysema. So, as the discussion ensues, it is important to kind of anchor it around that reality.

DR. HOLLINGER: Thank you. Yes?

MR. WALSH: The Alpha One Foundation has

established its own patient registry, and we hve just over 100 people that have never been on product before now. It is highly unlikely we are going to be able to recruit patients while there is possibility of product, to do a controlled study like this.

I do feel, however, that there would be support from the patient population to participate in dosing studies, 60, 90, 120, to ascertain whether we can optimize therapy or not. We have a registry that can identify people within certain parameters for a study that would be required, and I am certain that we could recruit patients to participate in that.

DR. HOLLINGER: And would you consider 30, 60, 90, 120?

MR. WALSH: Nobody has told us -- you know, if there is a 5-day half-life and at 60 we are seeing benefit from 35-49%, I don't think anybody would be interested in anything less than 60. I have been on 90 for the last 5 years. My twin brother is on 60 on a monthly basis, 240 on a monthly basis, and he has dropped down to 17%. So, I think there are a lot of patients who would go on a higher dosage in a study.

DR. BOYLE: Ultimately, one of the concerns here, if I understand it correctly, is not simply whether it is good science or not but whether or not we are

misunderstanding the data, that there are spurious correlations and basically we have something that doesn't work. If that is the case, and a better product or a different product comes along, and if we basically are looking at active-control comparisons -- because that is what it is going to be, there is going to be no placebo; it is going to be the other one -- then if, in point of fact, Prolastin and the other things are nothing more than a placebo and there is something better out there, that study is going to demonstrate that. Until that other product comes along, you know, following the thing that we have already said in question one, that, you know, basically equivalence is what we have established and whether it is active control or some other comparison to existing products is a reasonable standard I think protects us.

DR. MARTONE: I have some trouble with that last analysis. I mean, if the product is ineffective or non-efficacious, then anything you can compare to it that is ineffective or non-efficacious is just as good and, therefore, could be marketed. I mean, you could use water. So, I think there are serious problems with comparing it to a product you do not know is efficacious.

DR. HOLLINGER: Yes. Dr. Stroncek?

DR. STRONCEK: And, if a new company comes out with a drug they think really is effective, I don't think

they should be penalized by saying that they have to hve a randomized trial against something that is not effective and end up paying for the drug out there that is not effective. So, I think it is quite reasonable if a company came along and said they want to have a new product and they want to do a placebo-controlled trial, that is fine. If they want to say they don't want to do an active drug controlled trial, I think that is fine.

DR. HOLLINGER: In terms of the intravenous infusion, it sounds like there certainly is a sentiment for dosing studies perhaps, and new products looking at active-controlled evaluations using at least a licensed product. We have talked about the placebo already.

What about aerosol inhalation? That is a totally different thing. I mean, your numbers are off now. You don't know what it is. You want to just use your own logic about it -- you don't have those numbers. So, how are you going to assess the products that want to use aerosol inhalation? Yes?

DR. MITCHELL: For aerosol, I think it is almost important to look at dosing during periods when there might be an infection or something like that.

DR. HOLLINGER: Excuse me, I am sorry. They will keep the buffet open until 1:30, but I am going to ask the Committee members whether they really need to go -- I mean,

that is an issue that I want to clarify right now. We have to discuss another issue in closed session. That will go until three o'clock. I mean, that is what our plans are because I know people have planes to catch and have to leave. One possibility would be that we just go out and get a Coke or they will bring some things here, Cokes and cookies and we will just have a short break and then go right into that session, if that is needed. Is that okay with the Committee or not?

MR. DUBIN: Some people just had lunch from 12:00 to 1:00. Let's continue deliberating. Some of us need to check out, which we haven't done.

DR. HOLLINGER: No, we will have a short break. I just needed to clarify that. I am sorry I interrupted you, Dr. Mitchell. Go ahead.

DR. MITCHELL: What was the decision on that?

DR. HOLLINGER: The decision is that we are going to through this and then, after a short break, 15, 20 minutes to check out and do things, then we are going to come back here for the closed session. But we are not going to go for lunch specifically.

DR. MITCHELL: Okay. I was expressing my concern, if there is going to be an aerosol inhalation trial, about whether they should be looking at the dosages during an acute phase reaction such as an infection as being separate

from a maintenance dose.

DR. ELLISON: With aerosol we don't have this ten-year legacy of therapy behind us and I would think we could go with a placebo. Maybe Dr. Crystal could answer, but ten years ago did they have this debate about whether they should use a placebo, and we are rewriting history now or reliving the same debate?

DR. CRYSTAL: I was very interesting listening to the discussion. We -- we, meaning the community, which meant the FDA, the advisory panel, the NHLBI, multiple committees and many of us were on those committees for a number of years -- what everybody wanted to was a controlled trial, placebo-controlled trial. It was decided, and this was many, many years of discussions, that it was not possible to carry it off. It was not clear that we could do it. That was the decision as to why the biochemical efficacy was chosen. It wasn't because of lack of wanting to do it from a scientific point of view.

From the aerosol point of view, I have some prejudice since this is my patent and it belongs to NHLBI. So, keep that in mind with what I am going to say. I think aerosol is a terrific idea because it is 2% of the body weight and you save an enormous amount of the material. The problem is that the disease is in the interstitium. It is the wall of the alveoli. And, the only parameter that you

have, as has been pointed out, is the epithelial lining fluid because in the plasma it just goes away and distributes throughout the body. So, you are stuck in terms of efficacy parameters. Either epithelial lining fluid kind of parameters will be used, or inflammatory parameters, or it has to be mortality, FEV-1 and CT scanning. There really are not other choices for the aerosol. That is really what the crux of the issue is.

It was discussed somewhat at that time, but we didn't have the data that has now been published in terms of the aerosol, and so it wasn't really considered in terms of the approval at that time.

DR. HOLLINGER: Any other thoughts on the aerosol? Paul?

DR. MCCURDY: I am inclined to think that there ought to be a comparison trial of the aerosol versus standard therapy. The problem is that the placebo effect of an aerosol, and possibly the amount of coughing that might be induced and bring up stuff that you would like to clear from the lungs would be very great.

How you would design and carry out a blinded controlled trial where both groups get something intravenously and both groups something by aerosol and you sort it out, I don't know whether that would be a doable trial either. The clinical endpoints that Ron just

mentioned I think would be the ones to look at. From what we heard today, it might not take a very large number of patients or a very long period of observation to do that.

DR. HOLLINGER: It does make it difficult statistically, doesn't it, when you have totally different ways of administration, does it not?

DR. D'AGOSTINO: Well, one design is the individual gets both. Whether or not you are going to be able to get people to join the study and, you know, get a sham on IV and then get the aerosol and the other way around -- but if that happened, then you do have a way of analyzing the data. It oftentimes does happen in those studies though that the individual gets randomized and then gets treatment A, the aerosol, or treatment B, the IV and not any kind of sham procedure.

DR. HOLLINGER: But the sham procedure would be that one would get, say, active ingredient in the aerosol or the reverse.

DR. MOYE: Each subject gets the infusion and the aerosol. It is determined by randomization whether both are active, neither are active or one is active.

DR. D'AGOSTINO: And, if you can get people, you know, to join a study such as that.

DR. HOLLINGER: It is an interesting concept though. Yes, please? State your name and organization,

please.

DR. MUELLER-VELTEIR: My name is Guenther Mueller-Velteir. I am from Centeon. I want to make a comment on the possibility of doing a controlled study, active-controlled aerosol inhalation study against IV. I think that the sample size for such a study would be much higher than Dr. D'Agostino presented before because that would be an equivalence type of study, meaning that the difference to detect would be smaller than assumed in the sample size calculation made by Dr. D'Agostino. So, I think this would be a very hard study to do.

With regard to the intravenous infusion, if you link question number four to number one, I understand that the vote was that the biochemical efficacy of 11 microM would be accepted, and in this light I don't think that a dose-controlled study would add much more information because we know that the more we infuse into these patients the higher the levels will be. So, I don't think that this adds much more to the scientific information.

DR. HOLLINGER: Okay. Here there should probably be a dose level, I would think with any new product like the inhalation. Then it comes down to the sham procedure versus the other. I, actually, think the sham procedure sounds pretty good, personally. What do the other Committee members think? Anybody have any feelings one way or the

other? Yes?

DR. MITCHELL: I agree that having the two types of administration, one being a sham and the other being the active ingredient would be appropriate. But I think what the gentleman just said is something that we need to address if the only endpoints are going to be the amount of drug in the system and we are adding more, then we are going to say it is more effective. I think that our sense is also that there should be some clinical endpoints, such as the CT and so on, and I think that we have said that before.

DR. HOLLINGER: I get the impression most of the group would feel that you have to have something like that because the measurements are not going to be 11 microM. It is actually much lower than that. Any other comments on that question before we go to the last question? Yes?

DR. PIERCE: I think the Committee has already answered at least the first part of the last question. The second part deals with what should the role be of phase IV studies.

DR. HOLLINGER: Okay. The fifth question, for products already under study in phase II or III clinical trials -- these are already under study -- should FDA require modifications -- we have talked about those. And, (b) if not, should FDA require that product sponsors address these recommendations in phase IV post-marketing studies?

Anybody have any burning thoughts about that? Yes, please?

DR. WACHTER: I just wanted to go back to question four for a second.

DR. HOLLINGER: Go ahead.

DR. WACHTER: My name is Allan Wachter, representing Alpha One Pharmaceuticals. One of the problems that I am hearing is that if we require placebo control -- and I desperately agree that placebo-controlled trials are critical because we need a definitive answer, however, there is the ethical problem, do we tell patients when we are enrolling them for an aerosol study that the current therapy, Prolastin, is ineffective? Do we tell them that it is effective? Because if we are enrolling someone in an aerosol study we are trying to tell them that we have something better. And, if we are going to say you can't have Prolastin or one of the other products you are already implying that it is an inferior product. So, I think there is an ethical dilemma there when we don't have any significant data for Prolastin.

DR. HOLLINGER: Well, you presented some data earlier that said it is more cost effective, it is easier to give. So, there are a lot of other reasons to do it besides whether it is less effective.

DR. WACHTER: Oh, definitely. I agree. I am just asking what do we tell patients when we are enrolling them.

Is Prolastin an effective therapy or not an effective therapy?

DR. HOLLINGER: Well, you see that there are differing opinions even in this group. Yes, please?

DR. MOYE: In the absence of any clinical data, I think you have to say you don't know. You don't know if it is effective. That is why it is included in the study.

DR. HOLLINGER: That is why you are doing the study, which is what should have been done a long time ago. Mr. Dubin?

MR. DUBIN: I mean, it is pretty straightforward. You tell the patients you are looking for alternatives. When you enroll them in the study I don't think the implication is immediately that what you are doing is better. You are looking for an alternative. I think it would be a fairly unethical thing to do, to tell them that this is better. You don't know that. I think one thing that is clear is that the placebo study should have been done years ago, and we don't have that kind of hard data, but we do have a fair amount of anecdotal data, and we saw some of the mortality rates. So, we have some evidence. So, I don't think it is this cut and dried thing that anything that you are looking at is necessarily going to be better. It is certainly an alternative, and I think that patients you are looking to enroll in a study should be told

and it should stop there.

DR. FEIGAL: If you don't mind, I think you have already answered this question with question number one because you asserted that it was still appropriate for these products -- sufficient, I guess was the word in the question, to use the level of the drug. So, unless there are things that you want to add to the discussion of the first question, I think you have already answered this question and you might be ready to move on to the rest of the program.

DR. FINLAYSON: I would like to just imply answer the question the gentleman raised from the floor. What you tell the patient is that you are comparing your product to a licensed product.

DR. STRONCEK: In question five, when it says what products are already under study, is this just the IV preparations or is this the inhalation preparations too? Because I would agree with 5(a) if it is only including the IV preparations.

DR. HOLLINGER: It is only the IV because inhalation is not under phase II and III. Correct me if I am wrong, none of the inhalation products are under phase II and III. So, it is strictly the intravenous products.

Is it clear that we don't hve to answer 5(a)? We have done that already. So, I think we are done. So, we

are going to close. The Committee will come back in half an hour, 1:45.

[Whereupon, the proceedings were recessed to be resumed at 1:45 p.m.]

AFTERNOON PROCEEDINGS

DR. SMALLWOOD: During this time, Committee members may avail themselves of the refreshments there. We don't want you to pass out on us before we complete our business. Dr. Hollinger?

DR. HOLLINGER: There is a draft report. An intramural site visit was held in February, and that is what we are going to be discussing. So, initially we are going to have an organizational overview by Dr. Goldman and I guess John Finlayson. Then we will go for an overview of the two divisions that had the site visit.

Review of Draft Report of Intramural Site Visit

Laboratories of Hemostasis and Cellular Hematology and Laboratory of Hepatitis

Organizational Overview

DR. GOLDMAN: Thank you, Dr. Hollinger. Well, I thank all of you for allowing me to address you today. I am going to do a little more than just an organizational overview. I know that there are some of you out there who are new, and I welcome you, and I thought I would take this opportunity to reinforce that part of your responsibility on

the advisory committee that has to do with review of our research.

[Slide]

I thought what I would do is actually begin with literally the beginning, our mission. You have this in your handout. The mission of CBER is to protect and enhance the public health through regulation of biological and related products including blood, as you discussed this morning, vaccines and biological therapeutics according to statutory authority. The regulation of these products is founded on science and law to ensure their purity, potency, significant, efficacy and availability.

[Slide]

As a means to support our science-based decision making, we were mandated by a PHS order, back in 1955 when we were the Division of Biologic Standards, the predecessor of CBER, as well, we were also mandated to do research through a recent update of the FDA ACT of 1988 Section 903. The mandate from 1955 said that we shall conduct research on problems related to the development, manufacture, testing and use of vaccines, serums, antitoxins, and analogous products including blood and its derivatives. It shall conduct other studies to assure safety, purity, and potency of biologic products, to improve existing products and develop new products.

[Slide]

Under this mandate, the types of research, and this is mission relevant research, that we carry out includes research on specific products, which includes but is not limited to, mechanisms of action, potential toxicity, and surrogate measures of efficacy. These activities are associated with products that are under an active IND or license application.

We also do research on specific policy issues related to a product class, disease area, or therapeutic modality to provide the foundation for evaluating current and future biological INDs and license applications that are or will be submitted to CBER.

Lastly, we do research associated with the development of methods and standards to which products can be compared.

[Slide]

Some of the functions which research provides include facilitating the approval of safe and effective products; supporting decisions to withdraw products that are found to be unsafe; anticipating public health needs and supporting informed decision-making in the prevention of, and response to, public health crises, which I am sure you have probably dealt with quite a bit here on this Committee; encouraging industry-wide adoption of new technologies;

facilitating development of industry-wide standards and methods; contributing to improvement of existing products and the development of new products; and lastly, aiding in recruitment and retention of excellent scientists.

[Slide]

The broad mission-relevant programs in CBER address the following: They address product quality, biological assessments and clinical development and analysis. Some general issues under each of these areas include, for example, physico-chemical characterization under product quality, or detection of adventitious agents, as well, the standards and methods development fall under here.

Under biological assessments are included mechanisms of immunity or immunomodulation, biological responses and mechanisms of disease pathogenesis or product toxicity. Lastly, under clinical development is included clinical trial design, something I know you were discussing just a little while ago, as well as statistical and epidemiological analysis.

[Slide]

Now, the core research activities in the Office of Blood, and the laboratories you will be looking at today are in the Office of Blood -- these activities encompass many of those that I previously described in the previous overhead,

and these areas where research is necessary to support regulatory decisions include blood cells and cell-derived proteins, such as activation, storage, motility, adhesion or toxicity of platelets, leukocytes, hemoglobin-based blood substituted. It includes the coagulant proteins and their analogues, such as standardization of Factor VIII, Factor IV or von Willebrand Factor, as well as non-coagulant plasma derivatives and analogues which you discussed today, for example alpha-1 proteinase inhibitor.

Of course, the presence of adventitious agents in blood products and whole blood is also of paramount importance, and that includes detection of retroviruses such as the HIVs and HTLVs, hepatitis viruses, including hepatitis B virus, hepatitis C virus and currently the new flavor of the year, hepatitis G virus, as well as other bacterial and parasitic contaminants.

[Slide]

In terms of oversight, CBER's entire intramural research program undergoes rigorous review in multiple ways. This includes site visits of our laboratory research programs and the individuals who participate in those programs, every four years, by an external peer-review committee. We have been doing this for at least 15 years now.

Over the last two years we have performed internal

annual evaluation and prioritization of our research programs at the office level. Most recently, we have undergone an upper-level Center-wide review of research by an external blue-ribbon panel. This occurred in February of this year and was carried out, in fact, by a subcommittee made up of 26 scientists with outstanding credentials, representing academia, industry and other government agencies.

[Slide]

The strong endorsement for research, both at FDA as well as at CBER, has been echoed in the reports from two recent FDA Science Board subcommittees. The first includes the subcommittee chaired by Dr. David Korn, which reviewed research across the Agency and, as stated in that report, the subcommittee unanimously and emphatically affirms that robust, high quality programs of intramural research are essential components of the FDA's science base and are critical for supporting in a scientifically sound and rigorous fashion, the review and regulatory decisions made by the agency in discharging its mission to promote and protect the public health.

[Slide]

Again, this endorsement was reiterated just recently in the review of CBER research by a subcommittee headed by Dr. Les Benet. This is the one that took place in

February and, as stated in their penultimate report when the report is finalized, and it should be finalized in the next couple of weeks, and we will get out to all our Committee members the final report but, as stated, it is the consensus of the review committee that for our industry to receive prompt and appropriate regulatory reviews, as well as for the ability of our regulatory agency to respond to urgent needs, it is of utmost importance that the scientists in CBER have research capabilities at the cutting edge that allows them not only to understand the rapidly expanding methodologies to evaluate vaccines and biologics, but also so that CBER scientist reviewers -- this is the researcher/reviewer model that we currently use -- can interact with their colleagues and industry on a knowledgeable scientific and technologic basis so that the appropriate recommendations can be made.

[Slide]

As you are, I know, acutely aware and as you actually have been practicing for the last two days, your role as an advisory committee is certainly multifaceted. You provide technical advice on biological products, classes or groups of products. You provide advice on design of clinical trials; on use of surrogate markers for clinical endpoints; advice on interpretation of results of clinical trials; advice on risk assessment. Lastly, one of your

ancillary duties is the participation in the peer review of our intramural research programs and the research scientists in those programs.

[Slide]

For the four-year review of a laboratory a site-visit team is assembled. This usually includes one to two persons from the BPAC plus ad hoc experts in the field of those being reviewed. This then is the subcommittee of the larger advisory committee, BPAC, and this committee then is referred to as either the site-visit committee or the site-visit team. So, they are a subcommittee of you.

This committee is then charge to assess the quality and the appropriateness of the regulatory mission and the research being conducted. That includes the relevance of the research program, its scientific rationale, validity of approaches used in that program, the creativity of design and solution, and level of sophistication of that program as well.

[Slide]

In addition, we ask the site-visit team to evaluate the accomplishments of the individual scientists who are involved in these programs. That includes their experimental design and performance. This is their knowledge, skills and abilities; the demonstration of independence of effort; their originality; their stature and

recognition in their field, as well as their productivity.

[Slide]

We also ask the site-visit committee to provide us advice on current scientific direction of the research program; whether new directions should be considered; any changes in administration of the program or in level and utilization of the resources to that program. Lastly, we ask them to comment on the appropriateness at this time for certain personnel actions. These are actions, as you will discussion in closed session, that include promotions and conversions. We are not asking the Committee for a final decision. We are only asking for a recommendation.

[Slide]

At the end of the site visit there is an oral summary. Then there is a written report which is prepared by the chair of the site-visit team. In this case, the two chairs were Dr. Alving and Dr. Hollinger. The final report then is approved and goes on up and down the line so that it eventually gets back to the person who was reviewed.

[Slide]

This is where we are now. This is the task in hand for the current advisory committee. You have had six weeks to read this report, and in closed session we will discuss the report. The report, of course, includes the critique of the research program, the evaluation of the

researchers themselves, as well as recommendations for personnel actions.

After your discussions we will ask that you vote on the draft report from the site-visit team. Your choices are to vote to reject the report if you feel it is completely inadequate. You can vote to accept the report if you feel it is complete and accurate. Lastly, you can vote to revise the report if you feel that there is something that needs to be modified. If that is the case, then you would go on to modify the report and you would vote to accept the modified report. This, then, will be the culmination of your official participation in helping us to peer-review our research programs and the respective research scientists who carry these programs out.

I must say that in these times of diminishing resources for our Center, your help and evaluation is most valuable to the Center.

I hve given you sort of a general overview of the process of your participation in the review of our research, and with Dr. Hollinger's indulgence I would like to turn the podium over to Dr. Finlayson, who now will actually give you sort of the organizational picture for the laboratories which were actually reviewed and which you will be discussing today. Thank you very much.

DR. HOLLINGER: Thank you.

[Slide]

DR. FINLAYSON: I am showing this for only one purpose, which is to orient you to the divisions that we are going to be talking about. There are two things I should say. First, it is not completely correct and, secondly, it is probably invisible from where you are sitting and that is why you have a handout.

Before we start looking at a few little boxes in this multi-box thing that I want to call your attention to, I just want to reiterate one thing that Dr. Goldman said because it is very pertinent to the specific nature of the site visits that were carried out on February 26.

As he told you, albeit it went by very quickly, all of the laboratories in the Center for Biologics Evaluation and Research are reviewed on a regular four-year cycle. However, there are sometimes specific compelling needs that require review of other scientists or other groups to be melded into that review. Well, it turns out that in this particular pair of site visits we have a lot of melding. In fact, we have more melding than we had original visitees.

So with that in mind, I will direct your attention to this. The Center for Biologics Evaluation and Research has at present five offices, although even as we speak procedures are under way to meld this office and this

office. We need not concern ourselves with this because the three product oriented offices, Office of Blood Research and Review, Office of Vaccine Research and Review, and Office of Therapeutics Research and Review, are still product oriented, and will remain product oriented offices.

Here, in the Office of Blood Research and Review, the two divisions that we are concerned with are the Division of Hematology, the Director of which is Dr. Mark Weinstein, and the Division of Transfusion Transmitted Diseases, of which Dr. Edward Tabor is the Director.

[Slide]

We are now going to expand and look at the Division of Hematology. Dr. Weinstein is not here but the overview of the Division will be given by Dr. Basil Golding.

Now, in the four-year cycle it came out that the Laboratory of Hemostasis was up for its regular review, and we have two staff fellows in there, Dr. Chang and Chung. Actually, maybe I should introduce them. Dr. Chang, where are you? And, is Dr. Chung here? No? Okay.

However, in the Laboratory of Cellular Hematology, Dr. Jaroslav Vostol was being proposed for conversion from staff fellow status to permanent status and, therefore, needed a current site visit. Therefore, we melded Dr. Vostol into the review of the Laboratory of Hemostasis.

[Slide]

However, it turned out also that the research program of Dr. Tabor himself, and, as you will hear when he gives an overview of his Division, his program is concerned with hepatitis research, and needed to be reviewed. Subsequent to that, within the Laboratory of Molecular Virology Dr. Andrew Dayton was proposed for conversion from staff fellow status to permanent status and so he also was melded into this review. Dr. Tabor, could you let people see who you are? Thank you. And, Dr. Dayton? Thank you.

So, with that heterogeneous group that needed to be reviewed, we assembled two site-visit teams, with Dr. Linden actually serving on both of those teams and getting lots of exercise moving around from one location to the other. These two teams have prepared draft reports, which I assume that you have, and I would point out that they are simply draft reports until they have been accepted by the full BPAC Committee.

So, just to summarize your task as Dr. Goldman outlined it, the things that you are being asked are, one, whether you feel that the research program of the Laboratory of Hemostasis is on target; whether the staff fellows, Dr. Chang and Dr. Chung, are making progress toward that target; whether Dr. Vostol is recommended for conversion to permanent status; whether Dr. Tabor and his hepatitis program are of such caliber as to warrant his continued

supervision of doctorate level researchers; whether Dr. Dayton, who is within the Division headed by Dr. Tabor in the Laboratory of Molecular Virology, is recommended for conversion to permanent status.

Again, you have these draft reports and your options are, as Dr. Goldman pointed out, you can reject them out of hand; you can accept them as written; or you could vote to revise them, make those revisions and then vote to accept them with revisions. Unless you have any particular questions for me, I think we can go into the divisional overviews. Dr. Golding will give the first one for the Division of Hematology. Dr. Weinstein is on assignment in Europe even as we speak, so Dr. Goldman will present on his behalf.

Overview of Division of Hematology

DR. GOLDING: Good afternoon. Dr. Finlayson has mentioned many of the things that I was going to bring up so that makes my task easier and allows me to go through this very quickly.

[Slide]

As you have heard, the Division of Hematology is directed by Mark Weinstein, and there are three laboratories, the Laboratory of Cellular Hematology, headed to Liana Harvath, the Laboratory of Hemostasis, headed by Mark Weinstein who is the acting chief at this time, and the

Laboratory of Plasma Derivatives, headed by myself.

What we are talking about in terms of the cycle review is the Laboratory of Hemostasis, which was subjected to the site visit with two staff fellows being reviewed, and one staff fellow, senior staff fellow from the Laboratory of Cellular Hematology was also involved in this site visit.

[Slide]

So, just very quickly, what are the product responsibilities of these groups? The primary responsibility is for scientific evaluation of biological products related to blood. This includes cellular components. So, what we are talking about here for the Laboratory of Cellular Hematology, they regulate granulocytes, platelets and stem cells.

The Laboratory of Plasma Derivatives and the Laboratory of Hemostasis regulate proteins that are isolated from the blood or plasma. So, plasma derivative products include albumin, immune globulins, alpha-1 proteinase inhibitor that you heard about this morning.

The Laboratory of Hemostasis regulates coagulation products, mainly Factor VIII and Factor IX. We also regulate analogous materials that are derived by recombinant DNA technology. The approved ones are the Factor VIII and Factor IX, and there are some products in the pipeline. We also regulate materials that provide clinical benefit

analogous to blood-derived materials. What I am referring to here are products that are used for volume expansion. We also regulate devices used to prepare, preserve and to store blood products.

[Slide]

These are the current research projects in the Laboratory of Hemostasis. The two staff fellows that are being reviewed, Dr. Chang and Dr. Chung, are involved in projects which relate to these issues. So, the one issue is to oversee the development of Factor VIII standards, to resolve differences between the chromogenic and plasma-based assays for Factor VIII, and to develop a new assay for thrombin.

I would just like to mention that Andrew Chang and Sau Chung have both played a very important role in regulation and in developing research programs in this laboratory. They have both been in the program for four years, and our ability to maintain staff fellows with that standard is important for our ability to keep up with our regulatory and research objectives.

[Slide]

So, the Laboratory of Cellular Hematology has a section which focuses on platelet research, and the main focus is on platelet activation and on platelet prions. This group is headed by Jaroslav Vostol, who is a senior

staff fellow, and he supervises a Fogarty fellow, a staff fellows and two biologists. The regulatory products and issues that they deal with are platelets for transfusion, instruments for collection, devices for storage, platelet substitutes and derived products, and guidance for platelet testing.

As Dr. Finlayson has already pointed out, Jaroslav Vostol is a senior staff fellow. He is now in his seventh year as a staff fellow, which implies that this is the last year in which he can be converted to a tenured position. He has until November 1 of 1999 to be converted to that position. So, it is important and very timely that your recommendation be considered, and that will have a marked impact on his career with us. I would also like to emphasize that not only does he play a role in research and regulation, but he is one of the few M.D.s that we have in our Division and, as such, plays an important role in looking at adverse effects analyses in our Division. Thank you.

DR. HOLLINGER: The next overview is of the Division of Transfusion Transmitted Diseases and that will be made by Dr. Edward Tabor.

Overview of Division of Transfusion Transmitted Diseases

DR. TABOR: Good afternoon.

[Slide]

I was asked to give you a summary presentation of the Division of Transfusion Transmitted Diseases, actually an overview of the Division and a summary presentation. I am going to use my editorial purview here and emphasize the summary presentation so I can tell you some things about my laboratory and skip some of the overview.

[Slide]

I came back to Biologics, after an interval of a number of years away from Biologics, two and a half years ago, two years before the site visit. When I came back I brought my laboratory, that is I brought the personnel and all the equipment. We came from the National Cancer Institute, and NCI was extremely cooperative in allowing us to move everything. So, we really just set up the same lab. The agreement I had with the Center for Biologics was that we would continue to research and gradually, over a period of years, switch to research projects that were perhaps a little bit more standard CBER type projects.

Well, the laboratory has been set up administratively as a section in what is known as the Laboratory of Hepatitis but it is really the only laboratory in the Laboratory of Hepatitis at this time that is doing any research. We have staff of about postdocs and one technician.

[Slide]

As I said, when we came here we had a group of high tech, cutting edge projects that were really set up from the point of view of NCI, and we have gradually been switching over to projects that are more in line with what CBER is interested in.

But to summarize the mission of the laboratory, I would say it is to study the molecular biology and seroepidemiology of hepatitis B virus and hepatitis C virus. In particular, we have been switching to projects that deal with finding those viral mutations that allow these viruses in some cases to escape detection by licensed systems.

[Slide]

I wanted to emphasize the switch over from NCI because I have the feeing that in our presentations to the external review at CBER that this point was missed. For this site visit we were asked to review four years of work and, since we had only been here for two years at the time of the site visit, of necessity a lot of that was cancer related.

Now I would like to take just a very few minutes to tell you one of the projects from the site visit related to the seroepidemiology of the hepatitis B and C viruses to give you a flavor of what the laboratory is, and also to show you a little bit what a laboratory in CBER can do to creatively pursue the goals that are consistent with CBER's

mission.

[Slide]

We have been very interested in the hepatocellular carcinoma because of its connection with the hepatocellular B and C viruses But you might ask why is hepatitis carcinoma important to blood transfusion and blood recipients. Well, the reason is that people who receive lots of transfusions have a higher risk of hepatocellular carcinoma, and there have been two studies published in the last six months, one from Manucci's group in Italy, and one from de Shako's group in England, that have shown that hemophiliacs have an extremely high rate of hepatocellular carcinoma and all of that rate is associated with hepatitis C virus infection.

[Slide]

Now, in Japan, in the last quarter century there has been a marked epidemic of hepatitis C virus infection, but there has also been an epidemic, an epidemic increase in the incidence of hepatocellular carcinoma.

This slide that I made using IARC data covers the years up to 1987 but I have other data from Iazaki Prefecture showing the same thing in years 1975-1995. What is shown here is that the incidence of hepatocellular carcinoma has gone from about 2/100,000 to 41/100,000 in nearly a quarter century. In contrast, among Japanese Americans in Hawaii the incidence of hepatocellular

carcinoma has remained constant, around 5-8/100,000.

[Slide]

We set about to investigate this, and we were very fortunate to be able to participate in the Miazaki cohort study in collaboration with Dr. Sherry Stiver and Nancy Miller at the Harvard School of Public Health, and with Dr. Tsubouchi in Miazaki Medical School in Japan.

[Slide]

The Miazaki cohort study was a study to study the natural history of HTLV-1 infection and in Miazaki 27% of people have HTLV-1 infection. In investigating this population they found a village where 23% of the people have hepatitis C virus infection. When I heard about these two infections being so prevalent in that village, I wondered whether the role of co-infection could perhaps lead to a greater rate of hepatocellular carcinoma, and I suggested they look to see how many cases they had had. The study has been conducted in two villages, including this one village, of about 2000 participants seen in healthcare visits.

[Slide]

When they went to look, at my suggestion, to see how many HCC cases there had been, they found 10 cases in a 10-year period in this one village, from 1984 to 1993. We set about to study these, and we identified 5 matched controls for each of the HCC cases. We matched them by age,

sex, date of serum collection and HTLV-1 status.

[Slide]

What we found among the liver cancer patients was that about 90% of them had anti-HCV. We were only able to get a full battery of tests on 9 of them because of the lack of material on the tenth. In the controls only 18% had anti-HCV. It was a highly statistically significant difference. The only one of the liver cancer patients with hepatitis B was the ninth patient and there was very little in the controls.

[Slide]

Well, what we concluded from this part of the study was that anti-HCV was strongly associated with liver cancer in Miazaki, Japan, and that co-infection with HTLV-1 was very common in these patients but was not related to the high incidence of liver cancer.

[Slide]

To see how this affected that constant level of liver cancer in Japanese Americans in Hawaii that I showed you at the beginning, we participated in a study of Japanese American in Hawaii, in collaboration with Dr. Abraham Nomura at Kuakini Medical Center in Honolulu.

[Slide]

In this study, almost 6000 Japanese American men were enlisted who had been born between 1900 and 1919,

almost all of them born in Hawaii, all of them living in Oahu, and they were listed in the Honolulu Heart Study around 1965, and serum samples were obtained and frozen between 1967 and 1970.

[Slide]

We were able to identify 24 hepatocellular carcinomas between 1970 and 1992 in this population. These were identified by looking at the discharge records of all Oahu hospitals, and we were able to do this because only 1% of the 6000 men had left Oahu in all those years, and they were confirmed using the Hawaii Tumor Registry.

[Slide]

Each HCC was matched to 3 controls without cancer by age and date of serum collection.

[Slide]

Much to our surprise, we found that 71% of the HCC cases had hepatitis B infection compared to only 5% of the controls. There was no anti-HCV whatsoever among the HCC cases and almost none among the controls. We wondered whether this very low prevalence of hepatitis C virus infection in HCC cases in Japanese Americans in Hawaii could, in fact, be due to the fact that there just isn't much hepatitis C virus in Hawaii.

[Slide]

We were fortunate in being able to get the

cooperation of Dr. Frolich at the Blood Bank of Hawaii, and in data from over 6000 first-time donors there the prevalence of anti-HCV was only 0.5%, basically the same as that seen on the mainland of the United States. About 27% of these blood donors were presumed to be of Japanese ancestry because of their surnames.

[Slide]

So, what we concluded was that hepatocellular carcinoma in Hawaii is very closely associated with hepatitis B virus infection in Japanese Americans. In fact, hepatitis C virus infection is very rare in Japanese Americans in Hawaii, regardless of whether they had liver cancer or not.

It is possible that the absence of an increase in hepatocellular carcinoma incidence in Hawaii in Japanese Americans in Hawaii, contrasted to that seen in Japan, is due to the fact that hepatitis C virus infection is much less prevalent in Hawaii. It is certainly much less prevalent than in the pocket of high prevalence that we found in the village in Miazaki.

It is also possible that the ancestors of these Japanese Americans that came to the United States before the current epidemic of hepatitis C virus infection in Japan, and it is also possible that this virus just was not efficiently transmitted from one generation to another.

Anyway, this gives you an idea of the kinds of studies that can be done with the resources available in CBER, and it shows you how these resources can be focused to produce answers to important questions related to the viruses we are studying. Thank you.

I was just handed a note asking me to mention some of the work of the Laboratory of Molecular Virology with regard to Dr. Dayton's tenure application. The Laboratory of Molecular Virology is actually the jewel in the crown of the Division of Transfusion Transmitted Diseases, headed by Dr. Indira Hewlett. Like every laboratory in CBER, they have to do the research they do while carrying a very heavy load of regulation, in this case regulation of kits for the detection of HIV primarily.

It is a very active program of research in HIV, and Dr. Dayton's work in particular involves work on cellular responses to HIV infection. I am afraid I wasn't prepared to summarize this work but I am sure you can ask him questions since he is here.

DR. HOLLINGER: Are there any questions of the people that hve spoken, any issues?

DR. BUCHHOLZ: Yes, could the speakers give us an idea of what proportion of time is spent doing research and what proportion is spent regulating?

DR. GOLDING: Well, seeing I am up here, maybe I

can address it for the people in our group. But can I just make a correction? I said that this was Dr. Vostol's last year and a decision needed to be made this year either to keep him on as a tenured scientist or, in fact, to terminate him. His position ends November 1 of '98, not '99. I said '99. So, he only has four and a half months. So a decision of the site visit is then sent with a package to an internal review committee and that also takes time. So, I would like you to consider that.

In terms of time spent on research and regulation, in the Laboratory of Hemostasis there has been a chronic situation of under-staffing. As a result, the fellows involved, Sau Chung and Andrew Chang, I would say spend 80% or 90% of their time actually doing regulatory work and have a very small part of their time allowed for research, which is not part of the concept of the way we want to do things but we have priorities and we have to deal with the regulatory issues. As far as Dr. Vostol is concerned, what would you say the mix is? Dr. Vostol is spending 75% of his time doing regulatory work and 25% of his time doing research. So, these are staff fellows who are being asked to develop independent research programs and the subject of their work was part of the site visit from our Division.

DR. TABOR: I would like to answer your question and put it in perspective because I think there is such a

crisis at this Agency right now that you can't honestly answer the question without putting it into perspective.

With regard to Dr. Dayton, here we have an outstanding young scientist who should be spending at least 50% of his time on research, and was doing so until about I would say July or August or September of 1997, but since that time has been spending I would say more than 50%, and during the fall and early winter was spending close to 100% of his time on regulatory work.

Now to put it in perspective, the Division of Transfusion Transmitted Diseases, which has a history of being an outstanding scientific and regulatory division for decades, is now at 75% of its strength two years ago. When I came to this Division in September, '95 we had 12 more people than we have now. Now, some of those positions we lost and some of them we haven't. Attempts to hire and fill those vacancies since January 1, when the freeze lifted, have all been stymied. So, we are operating at very low strength and every single person is spending more than -- no, I shouldn't say every single person; a lot of people, most of the Division, is spending more than 50% of their time on regulatory work at present. There are some people who are spending only 50% or slightly less but, by and large, everybody is having to pitch in on the regulatory work.

Now let me tell you what the problem with that is. At present, at CBER research is justified by saying that the research has to be to back up the regulatory work. You have to analyze an outbreak, or find out what the problem is with a contamination. That is all very true, but the real truth that nobody wants to say now because Commissioner Friedman takes a slightly different approach, is if you don't have good research potential and resources, you don't get good people and you are going to have poor people doing regulation if you don't have research to attract the good people.

I will give you a case in point. Three days ago, the acting lab chief of the Laboratory of Immunochemistry -- that is not a lab you are reviewing today -- announced to me he is leaving to go to industry. And this was one of the rising starts of our Division, an outstanding researcher who had tremendous leadership potential and would take on regulatory job I gave him and do it well, is leaving to go to industry, and the reason is because he couldn't do research here. Those were his words.

I will leave you with that. We have a crisis. We have to have good people. We have to have good people who can do research. We need good people like Dr. Dayton and Dr. Vostol, and we need to give them the tenure they deserve, and we need to give them the resources and the time

so that they can do good regulation and good research.

DR. HOLLINGER: Yes, Mr. Dubin?

MR. DUBIN: Dr. Tabor, could you elaborate a little more? You kind of started down this path and there is a logjam, but it is not clear to us where that logjam is. Clearly, I think a lot of us understand that you need top-flight research people and they need a climate in which to do their work. But I kind of got half a picture and I am curious.

DR. TABOR: Well, it is partly logjam and it is partly not logjam.

MR. DUBIN: Is it the climate?

DR. TABOR: We don't know where the logjam is either, which is part of the problem. All we know is some of it is personnel; some of it is just the bureaucracy and its very nature. But the facts are as I stated them.

MR. DUBIN: Then may I ask you a question?

DR. TABOR: Yes.

MR. DUBIN: Is part of it the climate on the Hill? I mean, we have seen three attempts to really cut the FDA, three attempts that our organization have been involved in, in opposing.

DR. TABOR: Well, we had a 33% budget cut this year in CBER -- 33%. If you were running a grocery store on the corner and you had a 33% budget cut you would fire

everybody except your family members who are working in the store. It actually hasn't hurt us because we have so few people and everybody is doing regulatory work, no one is spending any money. So, in fact, this year has been a bumper year for us because nobody is able to spend any money because we had a 33% budget cut. That reflects the climate on the Hill, and you probably know as much about PADUFA as I do and all the negotiations that have gone on. Some of it is the climate within FDA, and I have probably been too outspoken about that already, but it is no secret if you read Science magazine that Dr. Friedman is not in favor of CBER research. Again, it has been published so I can say that.

MR. DUBIN: Right, but we are about to get a new FDA commissioner. That is what we are hearing.

DR. TABOR: Again, I probably know as little about that as anybody. So, I don't know.

DR. HOLLINGER: Any other questions by the Committee? If not, Dr. Smallwood?

DR. SMALLWOOD: We will now be moving into closed session. I would ask only those FDA individuals that have been identified by Dr. Goldman to remain. All other FDA personnel will have to leave, including Dr. Tabor, because you are under review. Those individuals identified by Dr. Goldman are Dr. Golding, Dr. Finlayson, Dr. Feigal, Dr.

Freis, and those members of my staff, Mr. Wilchek, Miss Wilson, Miss McMillan. We will also have with us Dr. Barbara Alving who was the chairperson of one of the site-visit committees.

[Whereupon, at 2:33 p.m., the proceedings were recessed, to be resumed in closed session.]

- - -

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

ALICE TOIGO