Food and Drug Administration
Center for Drug Evaluation and Research
Pulmonary Allergy Drugs Advisory Committee
Endocrinologic and Metabolic Drugs Advisory Committee

Rec'd 8/[illegible]/98

Orally Inhaled/Intranasal Corticosteroids and Growth in Children

July 30, 1998

Bethesda Marriott
Grand Ballroom
Pooks Hill Road
Bethesda, Maryland

Proceedings By:

CASET Associates, Ltd.
10201 Lee Highway #160
Fairfax, Virginia 22030
(703) 352-0091

PARTICIPANTS :

Pulmonary Allergy Drugs Advisory Committee Members:
James T. C. Li, M.D., Ph.D., Chairman
Leander B. Madoo, Executive Secretary
James N. Baraniuk, M.D.
Vernon M, Chinchilla, Ph.D.
Carroll E. Cross, M.D.
Mark C. Liu, M.D.
Molly Lee Osborne, M.D., Ph.D.
Curtis N. Sessler M.D
Stanley J. Szefler, M.D.
Brenda Conner
H. William Kelly, Pharm.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members:
Henry G. Bone, III, M.D., chairman
Kathleen R. Reedy, Executive Secretary
Roger D. Illingworth, M.D., Ph.D.
Robert A. Kreisberg, M.D.
Robert S. Sherwin, M.D.
Jules Hirsch, M.D.
Mark E. Molitch, M.D.
Jaime A. Davidson, M.D.

TABLE OF CONTENTS

TABLE OF CONTENTS (Cont.)

P R O C E E D I N G S [8:00 a.m.]

Agenda Item: Call to Order, Introductions, Opening Comments

DR. LI: My name is James Li and I would like to welcome everybody here today to today's deliberation, as well as a welcome for tomorrow's deliberation.

I am an allergist at the Mayo Clinic and chair of the Pulmonary Allergy Drug Advisory Committee.

Every advisory committee meeting is special, but I think that this meeting, this two day session is especially so. One reason for that is that this is, I believe, the first time that the Pulmonary Allergy Drug Advisory Committee has met jointly with the Endocrine and Metabolic Drug Advisory Committee.

I think the other more important reason why this is a special meeting is that we are now having an opportunity to discuss important products that affect probably over 30 million, you know, individuals in this country, mostly patients with allergy and asthma.

Just before we get started, I wanted to remind the group, our committee group, that in my view, at least, the overall aim of this two-day session really is to keep in mind the welfare of the individuals who use these products; namely, the intranasal corticosteroids and the inhaled corticosteroids potentially could use these products, in

other words, to safeguard the health and the safety of our patients.

But the specific purpose of this two-day meeting really is to discuss and make recommendations to the FDA about class labeling for intranasal steroids and inhaled corticosteroids. I just want to mention this at the outset because perhaps during the two-day meeting, we will have to kind of revisit that focus. And the idea is that our charge is very specifically to discuss and make recommendations regarding the class labeling of these products.

I think probably Dr. Jenkins will give us some of his thoughts about where he might like the discussion to go, but from my standpoint, I think that for the committee, we want to be reviewing the available information clinically and trying to make some recommendations based on our opinions of these medications as a class, as a group, rather than individually.

What I will mention also, again, maybe from the outset is that we have a really very exciting agenda today and tomorrow. Not only is it exciting but the day is going to be very full. In the interest of fairness then, I will, you know, ask all the speakers to keep their remarks to the time allotted to them.

I think one of my roles will be to at least have each of the speakers start on time and the speakers job will

be to end on time. If I happen to remind someone maybe that their time is coming to an end, I apologize in advance.

With that, I have introduced myself. I would like to go around the table and have each of the people seated at the table to introduce themselves, their affiliation and their role in today's meeting.

Maybe we will start over on the left.

DR. PURUCKER: I am Dr. Mary Purucker. I am one of the medical officers in the Pulmonary Division. Good morning.

DR. JENKINS: Good morning. I am John Jenkins. I am the director of the Division of Pulmonary Drug Products in CDER at FDA.

DR. MALOZOWSKI: I am Saul Malozowski. I am the medical officer at the Division of Metabolism and Endocrinologic Drugs.

DR. ALLEN: I am Dave Allen, a pediatric endocrinologist from the University of Wisconsin.

DR. HINTZ: I am Ray Hintz, pediatric endocrinologist from Stanford University.

DR. SHAPIRO: I am Gail Shapiro, pediatric allergist from the University of Washington, Seattle.

DR. BARANIUK: Jim Baraniuk. I am allergist here in town at Georgetown University.

DR. KELLY: Bill Kelly, professor of pharmacy and

pediatrics, University of New Mexico.

DR. CARA: I am Jose Cara, the section head of pediatric endocrinology at Henry Ford Hospital in Detroit, Michigan and member of the Endocrine Advisory Committee.

DR. BONE: I am Henry Bone, endocrinologist from Detroit, Michigan and chair of the Endocrine and Metabolic Drug Advisory Committee.

MR. MADOO: I am Leander Madoo, FDA, native Washingtonian.

DR. SZEFLER: Stanley Szefler, director of clinical pharmacology, National Jewish Medical and Research Center in Denver.

DR. CRIM: Courtney Crim, Pulmonary Critical Care, St. Louis University.

DR. KREISBERG: Bob Kreisberg, endocrinologist, Birmingham, Alabama.

MS. CONNER: Brenda Conner, director of business development for Matria Health Care and I am the consumer representative to the Pulmonary and Allergy Committee.

DR. BURMAN: Ken Burman, head of endocrinology at the Washington Hospital Center.

DR. CHINCHILLA: Vern Chinchilla, biostatistics, Penn State Hershey Medical Center.

DR. HIRSCH: Jules Hirsch, Rockefeller University, New York.

DR. OSBORNE: Molly Osborne, pulmonary and critical care at Oregon Health Sciences University and the VA in Portland, Oregon.

DR. LIU: Mark Liu, pulmonary, critical care, allergy, immunology at Johns Hopkins University.

DR. GROSS: I am Nick Gross, pulmonologist at Loyola University in Chicago.

DR. AHRENS: Richard Ahrens, both an allergist and a pediatric pulmonologist from the University of Iowa.

DR. FINK: Bob Fink, a pediatric pulmonologist at Children's National Medical Center in Washington, D.C.

DR. LI: Next, Mr. Madoo will read the conflict of interest statement.

Agenda Item: Meeting Statement

MR. MADOO: Hello. Good morning.

First of all, I would like to make some administrative notes.

Committee members will note that in front of them are blue folders, which contain the agenda. Appended to the agenda are an iteration of your colleagues present, as well as the consummately revised questions.

Also, I would like to thank -- we have a rather -- as Dr. Li alludes to, we have a rather dynamic meeting the next two days. We have quite a few people who have come from abroad to partake in the open public hearing. We would

like to thank them for their interest in this activity.

When we get to the open public hearing, it is especially important to articulate your manner of conveyance, how you were conveyed and whether or not you have received the payment for your participation. That relates to the conflict of interest matter.

On a sad note, I would like to note that our former consumer rep, Barry Mitchell, is ill and in the blue folders is a listing of her current address if any get well cards wish to be conveyed by the committee members.

Also, I would like to thank two people from the Pulmonary Division in particular for their outstanding efforts in making this meeting come to fruition; David Hilsiger and Dr. Mary Purucker. I thank them very much for their efforts, and also, obviously, my colleague, Kathleen Reedy.

Now on to the conflict of interest statement.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research, which have been reported the

participants, present no potential for the appearance of a conflict of interest at this meeting with the following exception:

Since the issue to be discussed by the committees at this meeting will not have a unique impact on any particular form of product, but rather have rights for implications with respect to the entire class of products, in accordance with 18 USC 208(b), each participant has been granted a waiver, which permits them to participate in today's discussion.

A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves and such involvements. Their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvements with any firm whose products they may wish to comment upon. Also, just by way of follow-up, as alluded to in the conflict of interest statement, this is a highly collaborative and engaging meeting here. so, everyone around the table, including guests and

consultants and guest speakers, is encouraged to contribute input .

Also, by way of facilitation of audience participation, you can note that there are three mikes on the floor. So, obviously, Dr. Bone and Dr. Li will be presiding over this meeting and at their discretion, they will acknowledge you and you may contribute.

Thank you for your interest in this meeting.

DR. LI: Thank you, Mr. Madoo.

Next on our agenda will be introductory comments from Dr. John Jenkins.

John.

Agenda **Item:** Introductory Remarks, Historical **Background, Objectives for Meeting, Introduction to the Class Label, Structure of Meeting and Speakers**

DR. JENKINS: Thank you, Dr. Li, and good morning.

I would like to welcome the members of the committee to today's meeting. In the interest of time, I am going to cut short some of the introductory remarks so I can get directly into the meat of my talk.

Before we move into the talk, I would like to first make some acknowledgements of people who have made this meeting possible. First , we have four invited expert speakers, who will be speaking to us this morning about various topics as background information for our discussions

over the next couple of days.

I would like to thank Dr. Hintz, Dr. Levine, Dr. Allen and Dr. Shapiro for their willingness to contribute to this meeting. They have been very helpful over the course of the past couple months in. putting together the agenda and we look forward to hearing their expert opinion abut the topics they have been asked to speak about.

I would also like to recognize and acknowledge four of the pharmaceutical companies who are here today, who have voluntarily agreed to allow their proprietary and/or unpublished data to be presented and discussed in today's open public forum. Those companies include Astra, USA, Glaxo Wellcome, Rhone-Poulenc Rorer and Schering Plough.

Their willingness to participate in today's meeting really made the meeting possible. Thank you.

Finally, as an acknowledgement, I need to acknowledge my colleagues at the FDA, who really have made this meeting possibly by all the hard work they have put in over the past almost year to bring this meeting to fruition. I am not going to read through each of the individual names, but they are a truly dedicated group of individuals and I am proud to call them my colleagues. Thanks for all your hard work.

I have quite a range of topics that I am going to try to cover in the next 30 minutes or so. So, I may be

going fairly fast through some of these subjects. We will get the chance to revisit some of these tomorrow morning when I return to give a brief overview of the discussion points and the proposed class labeling before the committee brings its discussion.

I would like to start this morning by giving you some historical perspective of what were the events and the facts that led to today's meeting, how did we get here and what are we here to try to accomplish.

Let me first start by trying to make sure that we are all on the same page. This is a list of the currently approved intranasal corticosteroids in the United States. On the left hand column you see the active moiety or the drug substance or sometimes referred to as the generic name of the products.

In the center column are the various trade names that you may recognize those products under. Some products have more than one trade name. And importantly on the far right hand column is a listing of the lowest age that the individual active moiety is approved for use for the intranasal route.

Let me point out that maybe not all the products for a given active moiety are approved down to this age range, but at least one product is approved down to that age . It is important to note that this meeting is very

appropriate to be considering the impact of these products on growth, since nearly all the products are approved for use in children as young as six and at least one product is approved down to the age of four.

Moving on, these are the products that are currently approved in the United States for orally inhaled corticosteroids . Again, the active moieties are listed on the left hand side. The trade names that you may recognize are in the middle column and, again, you will note that the lowest age for which these products are approved for all the products goes down to six years and for one product goes down to four years.

I should note that the asterisk that is beside dexamethasone on both of these slides refers to the fact that while those products are approved, they are not currently being marketed in the United States.

The other point I want to make about these products is that as a class they are a relatively new group of products in the United States. By that I mean that although dexamethasone was approved for intranasal and inhaled use in the early to mid sixties, the vast majority of the products that we are talking about today were first approved in the United States in the 1980s. And I think you can see as you look across the slide that a large number of the products we are talking about today have been approved

in the 1990s, some of which have only been approved in the last couple of years.

So, this is not a group of products that have been as a class on the market in the United States for a long period of time, although some of these have been on the market in other parts of the world for longer periods of time.

Let me just try to set a little bit of foundation about how these products are used and what the current practice guidelines for use of these products are in the United States. This will be of no surprise to the members of the audience and the committee, who deal with asthma and allergy on a regular basis, but I wanted to make sure that everyone kind of had the same common foundation, ground to work from.

First of all, corticosteroids in asthma, as many of you are aware, over the past decade or so, asthma has become recognized as a chronic, inflammatory disease of the airways. Also, despite increasingly available therapies for asthma, the incidence, the morbidity and the mortality of asthma in the United States and other developed nations has been increasing over the past several decades.

It has been estimated that approximately 4.8 million children in the United States have asthma. So, again, this is a very appropriate topic to be considering

today since many of these children are treated with corticosteroids or could be treated with corticosteroids.

Finally, based on the growing recognition of asthma as a chronic, inflammatory disease, there has been a large push over the past decade to emphasize long term anti-inflammatory treatment for the improved management of patients with asthma. The acronym that I have here stands for the National Asthma Education and Prevention Program, Expert Panel Report 2, which is a group put together by the National Heart, Lung and Blood Institute.

They issued their revised guidelines for the diagnosis and treatment of asthma last year and a quote from that document emphasizes the point that inhaled corticosteroids are the most effective long term therapy available for mild, moderate or severe persistent asthma.

Moving a little deeper into that expert panel report, they recommend a stepwise approach for the management of asthma. Step 2 in their paradigm is a condition that they refer to as mild, persistent asthma. This, as many of you know, reflects very mild disease and their recommendation is that even patients with this very mild stage of the disease should be receiving daily anti-inflammatory therapy.

In both adults and children, they strongly recommend the use of low dose inhaled corticosteroids in

these patients as maintenance therapy, with the important caveat that for children they recommend that a trial of chromalin or nedocermil (?) may be tried first in children before moving on to the inhaled corticosteroids. And they also suggest that that may be considered in some adults.

Steps 3 and 4 in this paradigm are moderate and severe persistent asthma and the important point here is that inhaled corticosteroids are recommended as the backbone of anti-inflammatory care for those patients in all age groups .

The expert panel report also addresses the issue of inhaled corticosteroids in growth. Their conclusions were that the potential risk of inhaled corticosteroids are well-balanced by their benefits. They also concluded that the majority of the studies of the use of inhaled corticosteroids have not demonstrated an effect on growth, but a few have identified growth delay.

Some caution, for example, monitoring growth, stepping down therapy when possible is suggested while this issue is studied further. The key phrase that I want to emphasize is this, while the issue is studied further, I think there are quite a few-very well-designed studies that have come to light over the past couple of years that this panel did not have access to. That is one of the reasons we are holding this meeting today is to review these new data.

Moving on to corticosteroids in allergic rhinitis, rhinitis is also an inflammatory disease. It is very prevalent in the U.S. population and it is also very prevalent in children in the United States.

Allergic rhinitis may generally be considered to be a fairly benign disease on its own, but it does cause significant morbidity and can exacerbate some other more serious conditions, such as asthma. There is currently a practice parameter being published by the Joint Task Force for Practice Parameters of the Joint Council for Allergy, Asthma and Immunology.

We were privy to a June 28th draft of this document, which is a practice parameter for rhinitis. I wanted to put in context what the expert opinion leaders in the field are saying about corticosteroids and allergic rhinitis. Their opinion is that nasally-inhaled corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis and are appropriate choices for first line treatment, particularly if more severe.

They recommend a stepwise approach to managing allergic rhinitis in children, the first steps being allergen avoidance and supportive care. They then recommend moving to oral antihistamines and oral decongestants or intranasal chromalin sodium, but they also recommend

intranasal corticosteroids as part of their treatment paradigm:

The Joint Task Force document also addresses the issue of systemic adverse effects of these products. In their opinion, except for intranasal dexamethasone, these agents are generally not associated with significant systemic side effects and they state in their document that it is their opinion that extensive clinical and toxicologic studies have documented their safety, meaning intranasal corticosteroids, in long term usage in children and should not be frightening to clinicians or parents.

Again, we think that there are some data that have come available that this group did not have access to, but I should emphasize that we in no way today are trying to frighten clinicians or parents about the use of intranasal or inhaled corticosteroids. I will address that topic a little more in just a couple of minutes.

Let me now move to give you some background on the Pulmonary Division activities related to this class of products. This class of products was first transferred to our regulatory authority in April of 1994 from another division within the agency. Almost immediately upon receiving these products we initiated a review of the approved labeling for the products at that time. And in 1995, we issued a guidance document to industry asking that

they update their labeling to make the labeling more consistent or more reflective of the available .data.

Specifically, that document asks the companies to update the clinical pharmacology section of their labeling, as well as the adverse event section to reflect accumulated safety data that may have been derived since the approval of the product and we asked for a particular focus on the systemic effects, for example, effects on the adrenal axis.

The labeling guidance also tried to standardize the indication for these inhaled corticosteroid products across the various products. We tried to standardize some parts of the warning section and some parts of the dosage and administration section.

Finally and importantly in reference to this meeting, we referred the sponsors to the Agency's 1994 Pediatric Labeling Rule, asking that they update the pediatric use section of their label to reflect current data. For those of you who may not be familiar with that initiative, the Pediatric Labeling Rule, the Agency over the past several years has had a broad-based initiative to try to improve the labeling of drugs for use in children.

One of the first parts of that initiative was the 1994 final rule that is commonly referred to as the Pediatric Labeling Rule. The rule specifically addresses the pediatric use subsection of the labeling.

That rule actually does several things and I have listed some of the things that that rule did, but the one I really wanted to focus on is here at the bottom in that that rule required sponsors of approved products to examine the existing data to determine whether the pediatric use subsection of the approved labeling should be updated.

We have seen a fairly dramatic response to this labeling rule in the Pulmonary Division. We have approved a large number of pediatric efficacy supplements over the past several years. And I think it is exemplified by this slide where I have noted recent approvals for intranasal and inhaled corticosteroids for use in children.

The point I wanted to make here is that, again, I think the timing of this meeting is very appropriate since many of the products that we are talking about today have only been approved by the Agency for use in children over the last couple of years. So, again, I think the timing of today's meeting is very appropriate.

Some other activities that spurred this meeting -- and I am now getting to probably the pivotal one that brought us here today -- was that in 1996 and 1997, the division received two separate applications requesting the over-the-counter switch of intranasal beclomethasone for the treatment of seasonal allergic rhinitis. While those applications were being reviewed in the middle of 1997, we

received the report of a study that you will be hearing more about this afternoon and tomorrow morning, which was a study of intranasal beclomethasone at a dose of 336 micrograms per day in prepubescent children to assess the effect on growth.

We were quite surprised by the results of the study . First, there was a statistically significant decrease in growth velocity in the treated patients versus a control group and that effect was observed as early as one month after initiating treatment.

The second point that we were surprised by and somewhat disturbed by was the fact that in that same study, no significant impact on HPA axis function as assessed by AM cortisol or following ACTH stimulation testing were observed. In other words, the adrenal function testing was not predictive of the growth effect.

That gave us pause because most of the currently approved product labeling with regard to systemic effects of these products is related to adrenal function testing and now we had evidence that it was not predictive of important systemic adverse events. An advisory committee meeting had been scheduled to review these over-the-counter switch applications, but by mutual agreement with the sponsors, that meeting was cancelled while we reviewed this new data.

Now, during that same period of time in 1996 and 1997, the Agency was also receiving other positive growth

studies for other active moieties. These studies were being submitted to the Agency either in response to previous Agency requests that sponsors do these studies postmarketing or they were submitted as part of new drug applications.

Given the accumulating data that the division had available from these unpublished studies, we initiated a comprehensive review of the available growth data for inhaled and intranasal corticosteroids. The multidisciplinary working group that I mentioned earlier was formed approximately a year ago and charged with the task of reviewing this field.

That group on completing its review concluded that based on the available data, it would be recommended that we initiate class labeling for these products with regard to their potential impact on growth in children. Once we made the decision to go forward with the proposed class labeling within the Agency, we decided to bring that issue for discussion before today's meeting so that we could have an open public discussion of not only the proposed class labeling but actually more importantly these new unpublished data.

Let me briefly review for you what do the current product labelings say with regard to growth in children. Well, actually, if you look at these labels as we have, you will find that there is a real hodgepodge of statements in

the labeling for currently approved products. Some products make no reference to growth in their product labeling and those products that do make statements related to growth have no consistency in the statements that they make.

Most of the statements appear in the precaution section and I have listed a summary of the types of statements that appear. Not all of these statements appear in any one product label. You will see that many of the statements are associated with a possibility of growth suppression with extended use or excessive doses.

Some refer to the effect of oral corticosteroids. Some talk about particularly sensitive individuals. Some do make recommendations for growth monitoring and some do recommend weighing the benefits of therapy versus the risk.

Basically, the same is true for the inhaled corticosteroid current labeling with regard to growth. Here, one product makes no specific reference to growth in its labeling and the products that do make reference have a variety of statements, although they do tend to have more statements in their labeling with regard to growth.

These tend to appear in the adverse reactions, the precautions and the dosage and administration section. Most of the statements are very similar to the ones I just went over. Two new ones that appear in the inhaled corticosteroid labeling, there is a reference that growth

suppression can occur due to inadequate asthma control that appear in some of these labels and the last one here is a recommendation that patients be maintained on the lowest effective dose.

I made the point earlier that we were given pause by the finding that the systemic adrenal function testing that is incorporated in the labeling may not be predictive of other systemic effects. That gave us pause because it means that maybe our labeling is not very predictive of these systemic effects.

This is a run down of the current labeling and what assays of adrenal function are included in those current product labelings. You will see that for most of the products, they rely on either AM cortisol levels or six hour ACTH stimulation testing.

Some products still have fairly old tests and only the most recently approved new active moiety, mometasone(?) has some of the more potentially sensitive tests, such as urinary cortisol and 24 hour plasma cortisol AUCs. The most important point, I think, is at the bottom, that only two of the twelve current products have any information in their labels about HPA axis function in children.

Basically, the same is true of the inhaled corticosteroids . Most products rely on ACTH stimulation testing, although one product has no specific data with

regard to adrenal function testing in its label. But more importantly, again, at the bottom, only two of the eight product labels have any reference to data from children for adrenal axis function.

Let me move now to the objectives for today's meeting. I am going to run through these fairly quickly. First, we want to have a critical review of the available data in this public forum, including the recently completed unpublished studies that you will be hearing about this afternoon and tomorrow morning regarding the potential for these products to growth suppression in children.

We would like to hear your expert opinion evaluating the short and long term clinical significance of these data. We would like to hear your comments regarding the proposed class labeling for these products. We would also like to review the apparent insensitivity of basal and stimulated plasma cortisol levels as predictors as growth suppression and we would like to discuss the potential impact these new data may have from a regulatory perspective on requirements for new products that have not yet been approved in the United States.

For example, we will be interested in your opinion regarding whether a growth study should be required before approval for these products, whether a growth study should be required as a Phase 4 commitment and also whether

sponsors should be required to determine the lowest effective dose of their product before the product is approved.

This does not always occur in drug development. Products that do not have a narrow therapeutic index often are approved at doses that are safe and effective, but the dose may not necessarily be the lowest dose because that may not have been studied in a rigorous fashion.

A corollary to that would be we would like to hear your comments about what data the agency should request from sponsors of currently approved products with regard to growth if those issues have not already been adequately addressed.

The final two parts are to seek your advice on how to design and conduct and analyze studies to assess the impact of this class of drugs on growth in children and, more importantly, we are really interested in hearing any ideas you may have on how to ferret out whether these products have any impact in the long term in children. For example, do they impact on the attainment of final adult height?

Now, there are some important caveats to the objectives that I want to make very clear. And I think Dr. Li started with some of these this morning. First, FDA is not suggesting that orally inhaled or intranasal

corticosteroids are unsafe for use in children. I want to emphasize that point very strongly.

We are also not considering restricting the use of these drugs in children at this time. We are seeking to ensure that this class of drugs is properly labeled with regard to potential growth suppression in order to inform health care providers and to promote the safest use of these drugs in children where therapy is indicated.

I can't emphasize these two points enough. We are not suggesting that these products are unsafe for use in children. We are trying to inform the health care community and patients about the available data and also promote the safe use of these products.

We are not trying to induce steroid phobia as some have been concerned that we are trying to induce or may inadvertently induce.

Another key point that Dr. Li touched on is that we consider this to be a class issue. We are interested in focusing on this today as a class issue for all orally inhaled and intranasal corticosteroids. While it is possible that different products may be associated with differential potential for growth suppression when used in children, rigorous, scientifically valid, comparative assessments are not possible given the presently available clinical database, in our opinion. And we would really like

to focus today's meeting on discussing these products as a class.

To carry that comment one step further, FDA considers the available data inadequate to support rigorous, scientifically valid, comparative claims or promotion statements regarding the potential growth effects of the various approved active products. Comparative claims or promotions will require data from adequate and well-controlled comparative clinical trials. Cross study comparisons are inadequate to support such claims or promotions.

And a final caveat is that due to the time constraints on today's meeting, we have chosen not to focus on other important questions that are obvious with regard to this class of drugs. For example, we have not chosen to focus today's discussion about trying to determine what is the most sensitive predictive test of systemic activity of these products and we have chosen not to try to discuss other potential long term consequences of use of these products; for example, osteoporosis in adults.

If necessary and if the data warrant in the future, we may hold additional meetings to discuss those topics.

Now, at this time I am going to very quickly run through the questions or discussion points and the proposed

class labeling. The questions are in the handout. So, I am not going to spend much time reading these.

The proposed class labeling that the agency has drafted is not in your current handout but we plan to have that available for the members of the audience tomorrow. The committee should already have that in their package.

The first question that we are asking the committee to discuss is whether or not the available data are sufficiently compelling to support class labeling for all intranasal corticosteroids, regarding their potential negative impact on growth velocity in children. And we are asking for your comments on the proposed class labeling drafted by the Agency.

The proposed class labeling for these products is nearly identical between the two classes, intranasal and inhaled, and it generally adds statements to the precaution section, the pediatric use subsection of the precaution section and the adverse event section. I am not going to try to read through this at this time because of time constraints, but I think you can get the general gist that what we are saying is that this class of products have been shown to cause reductions in growth velocity when administered to children and that the risk could be weighed against the benefits.

The effect on growth has been seen in the absence

of laboratory evidence of adrenal suppression, which suggests that adrenal suppression may not be very predictive of growth suppression. The long term effects are not known and we also don't know about the potential of catch up growth following discontinuation of these products.

We recommend that children receiving these products should be monitored for their growth and that the potential effects of prolonged therapy should be weighed against clinical benefits and the availability of alternative treatments. That is, to me, good standard clinical practice and that to minimize the systemic effect of these products, patients who require these products should be titrated to the lowest effective dose.

I think you will see that these statements are not anything out of what would be considered good clinical practice for the use of these products and, in fact, they are very consistent with some of the expert panel recommendations.

Finally, we add information in the adverse event section about the impact of these products on growth in children and, again, recommend that children who are being treated with these products be monitored for their growth.

I know that that was a quick run-through through that proposed labeling. We will go through that in more detail tomorrow, but at least you have a flavor for the

proposed labeling.

The second question that we are asking the committee to discuss is basically the same question as No. 1, now focusing on orally inhaled corticosteroids.

The third question we are asking the committee to comment on the need to study the lowest effective dose of new products prior to approval and we are also asking you to comment on what should be done for currently approved products where the lowest effective dose has not previously been established.

Point 4, we are asking you to comment on whether we should require growth studies of new products prior to approval or whether we should ask for a Phase 4 commitment for a growth study after approval. And we are also asking you to comment on what data the Agency should request from sponsors of currently approved products where the effect on growth has not adequately been studied.

Next, we are asking you to comment on the features that you think are crucial in the design and conduct of a growth study and we have listed some of our ideas that we are interested in hearing your comments on.

Sixth, we are asking you to give us some advice on how can we assess the long term impact of these products on growth, particularly focusing on final adult height.

In the last couple of minutes, I am going to run

very quickly through the agenda, just to give you an overview of where we are going for the next couple of days. This morning's session can really be considered a background session. We are going to have talks on normal growth and development in children from Dr. Hintz; HPA axis assessment in children from Dr. Levine; a talk on the effect of corticosteroids on growth in children from Dr. Allen.

We are going to hear a talk about how these products are being used in the pediatric community from Dr. Shapiro and then we are also going to hear some introductory comments about design and conduct of growth studies, again, from Dr. Hintz.

There will be time for questions and answers after those talks.

This afternoon's agenda allows the companies that I mentioned earlier, who have these proprietary data, to make presentations to the committee, giving their interpretation of what the data show with regard to growth. I am not sure what order these companies have been assigned. I put them in alphabetical order.

This afternoon, we will have the open public hearing where several people have requested time to speak from the floor and there will be time before we close this afternoon for some open committee discussion.

Tomorrow morning's agenda is really the FDA

perspective on the available data. You will be hearing a brief introduction from Dr. Purucker, who is the chair of the working group within the Agency that has been evaluating this topic.

You will hear some epidemiologic background and actual use data, as well as some adverse event reporting data from Dr. Graham from our Epidemiology Branch. Dr. Worobec will give the material that is available in the published literature and then Ms. Elashoff will give some statistical issues that have become apparent to us as we reviewed the design and analysis of growth studies.

Then Dr. Saul Malozowski will review the proprietary growth studies that will be reviewed by the companies this afternoon and give the Agency's interpretation of these data.

Dr. Purucker will return for some summary and conclusive remarks and recommendations. There will be time for questions and answers from this working group.

Then, finally, tomorrow afternoon's session is really devoted entirely to committee discussion of the data, as well as the questions that we have put before you for discussion. I will return actually tomorrow morning before lunch. I will run through the questions again. I will run through the proposed class labelings in a little bit more detail than I did this morning and then we will open it up

for committee discussion before ending tomorrow afternoon.

Thanks for your attention.

DR. LI: Thank you very much, Dr. Jenkins, for those very clear opening remarks.

I guess if I would pick out a phrase that I believe gives us guidance for the overarching theme of our two-day meeting, it is the term “safe use,” that we here today and tomorrow are interested in evaluating and recommending the safe use of intranasal and inhaled corticosteroids .

With that, I am very pleased to introduce Dr. Hintz as our first speaker, who will be giving us really an educational overview on the issues of growth and steroids in children.

so, Professor.

Agenda Item: Growth and Development in Children

DR. HINTZ: At the end of this meeting, we will pass around a quiz, which will include how do you spell Dr. Malozowski's name.

My assignment in the next 30 minutes is to review all of growth and development in childhood and I will tell you to begin with that I am-going to fail that, but at least I will give it a good try.

so, this is the material I hope to cover in the next few minutes. I would like to go through the control

mechanisms, the growth in children, how do you assess growth, the use of growth charts and standards, talk about catch up growth, height prediction and, finally, do a little bit of hormonal influences and markers of growth probably as an introduction to Dr. Levine's more extensive talk on this.

So, first of all, there are multiple influences that control growth. It isn't a simple matter. Now, this is sort of an endocrinologist's viewpoint and, in fact, it is probably best to start from the bottom up on this slide. This little coil there was my cute idea for saying genetics and DNA probably have the strongest influence on growth. We will get back to that when we talk about height prediction.

But there are other metabolic tissue growth factors and particularly nutritional issues that can affect it. Those of you in this room expert on allergy and immunological diseases know that many of these can, in fact, influence growth by themselves, irrespective of any drug that might recur.

Then in addition to that, there are hypothalamic factors controlling the secretion of pituitary hormones, growth hormone by way of its intermediary insulin-like growth factor, TSH by way of their intermediary areas of T3 and T4, corticosteroids and the gonadotrophins stimulating estradiol, testosterone and other sex steroids, all have an influence on growth.

Then, in addition, over here is insulin itself, which, obviously, can have an influence on growth. So, this is a very much -- it is a well-integrated system, but there are multiple components to it, which make studying any one of these legs difficult to try to make a conclusion as to what is going on.

As you well know, the corticosteroids really are -- by experimental evidence, you have to have an adequate amount for growth, but that even a slight excess can inhibit the rate of growth.

Now , Professor Karlburg in Sweden first presented this kind of a model of growth in which he said that this could really be analyzed into three separate phases of growth. Actually, if you want to look before the birth of a child, there is a prenatal phase, too, and that is that there is an infant phase over the first two years, which is very rapid in the first year -- those of you who remember your own children's growth -- and then tends to slow as you get into the second year of life.

There is a childhood phase, which takes over, beginning about six to twelve months and then gradually becomes the dominant form. And then finally -- and this is actually drawn in perspective -- is the pubertive growth spurts that most of us remember and we remember it as being very hectic. But the fact of the matter is it is actually

the smallest component of the three.

So, how do you assess growth? What are the mechanisms we have? And that is -- unfortunately, we don't have a magic way of doing that. SO, it really boils down if you want to assess growth, you have to have careful measurements of height. And the first method that I am going to discuss a bit is a stadiometer. This is a good/bad slide. On the left is, unfortunately, what most general pediatricians, and I suspect a lot of allergists and immunologists, have in their office, which is the combined -- let's get the weight and height at the same time.

There are several problems with this. First of all, the stick at the top is not truly a rigid right angle. so, it can be almost anywhere within a 90 degree angle and people will say, ah, that is good.

Second of all, you really don't have anything to back up to and get the child stable. Then, third, down here is an unstable platform, so that by their very nature, kids are going to crouch just a little bit because they feel that moving.

On the right side is a stadiometer. I don't know that there is any particular brand of this, but actually you can do stadiometry with a very simple methodology if you have a carpenter's right angle rule and a wall and a tape measure. This is the way I used to do it when I was in the

Air Force.

But in this modern day and age, of course, we have better technology but it still boils down to the same thing; that is, a stable platform and a right angle up here. Now, I have to say that this picture is bad because, in fact, you should have the child backed up against the wall and carefully position them and in most pediatric endocrine studies, where we have tried to look at growth, we have had the stadiometry done three times independently for each type measurement.

Now, just to show you that this is not a new technique, this is actually a drawing by Goethe, the German poet and philosopher of the 18th Century. One of his many jobs -- poets and philosophers -- there may be a few in the room -- actually have to have a way to make a living. So, Goethe's way of making a living is he worked for the government of the Duchy of Saxony. And one of his jobs was to go around measuring army recruits. And you can see that he actually has a very good -- there is a very good technique here, a stable place to stand. It is right up against the wall.

There is a right angle here and I don't know whether that is Goethe or whether he just did the drawing. so, this is not rocket science, as they say, but it is important.

Now, another way that has been used in pediatric endocrinology, and I have, you know, seen some of the articles in which this is also used in this setting, is knemometry. And, unfortunately, I couldn't find my slide of a anemometer, but basically this is a measurement, which just looks at the lower leg length so that the foot is positioned and then you measure to the top of the knee and this can be quite accurate as to -- accurate down to the 10th of a millimeter range as opposed to stadiometry, where you can get down to, you know, 1 or 2 millimeters but not much better than that, the knemometry can be done.

In the hands of an experienced operator with good equipment -- and I will come back in a minute to that point -- you can, in fact, see growth over quite short time periods, you know, as short as a week or so, can give you a reproducible index of the growth of at least the lower leg.

Now, I want to emphasize that knemometry has several problems. One is the equipment is rather expensive. This is not something that you are going to -- unlike the stadiometer, which you could whump up in your work shed using some simple things from the hardware store, this is not simple equipment. So, the equipment tends to be relatively expensive.

My impression is it is not widely distributed either in pediatric endocrinologists or certainly not in

general pediatricians and certainly not in allergists. So, that is the first problem.

The second problem is it does take an experienced operator. There is quite a bit of variability if you look at the studies where they compare the same equipment, the same child but two different operators. So that it is crucial that if you are going to use this, you have someone who is experienced in the use of it and you have the same person doing the measurements every time the child comes in, which can be a problem if you have a long term study.

But actually the biggest problem that has come up, and this has been reproduced by a number of different studies, is that although you can use this to show short term changes in growth rate, that growth rate does not correlate particularly well with the overall linear growth rate of the child.

So, although you might conceive of using it and it has been used in showing short term effects of steroids on growth rate, you cannot use that data to then extrapolate as to whether or not this is going to have an effect on long term growth.

I would also like to emphasize the point that you need longitudinal observations. I mean, this is obvious if you are going to be looking at growth rate. We are talking not just months but even years here. Now, this is an old

slide but it just illustrates a group of children who we later on diagnose as constitutional delay. These are children who will eventually go into puberty late. But they present to pediatric endocrine clinics not infrequently as being short children.

If you look back, you can see that they, in fact, right about the time that Professor Karlburg said while you are switching over from the infant mode to the childhood mode of control of growth that they have a slip of the gears . Then they actually grow quite reasonably at rates to that .

so, if you are trying to look at an influence of a pharmacologic agent on growth, you really have to have longitudinal observations. Now, pediatric endocrinologists, of which there are several in the room, argue about this all the time as to whether six months are enough, is a year enough, but I think that is the ball park where it begins to become rational. Certainly three months or two months or one month, unless you are using knemometry, doesn't give you reproducible data. And I have already discussed some of the problems in trying to use knemometry as your primary goal.

Then the other thing that is extremely important is assessing the pubertal status. Now , that first of all boils down to Tanner staging. Now , the reason. for this is that there is quite a bit of variability in when puberty

occurs and how rapidly you go through puberty,

so, this is a slide that you will get familiar with of growth rates and this is showing the affect on early maturers versus late maturers. So, your conclusions about whether a child is growing at a normal rate or not can be influenced quite a bit by the status of puberty. For instance, there is this prepubertal dip, so-called, shown quite well in this curve, in which children that are not yet quite in puberty but are going to be in the succeeding years, who actually have a significant fall off in growth rate.

If you were doing your study looking at pharmacological intervention, you would conclude that if you started the drug here, you would conclude, oh, my God, I have a major effect on growth rate, but, in fact, that is just part of the natural course of events. Then the other obvious point, of course, is that if you looked at your pharmacological intervention at this point or that point and just before the pubertal growth spurt and the growth spurt happens during your study, again, you would draw completely the wrong conclusions.

So, you need to assess puberty in some way. Now, this is -- and actually I decided not to try to teach you all about Tanner staging because most of you know about it or can easily learn about it, but this is just boys of the

same age lined up to show how variable puberty can be and you can see that at this -- children are -- is that 11? I can't read it, Marie -- I think the boys -- 12, okay -- that this is a group of four 12 year old boys.

This is actually from Tanner's work in England and you can see that they go all the way from clearly -- completely prepubertal all the way to essentially adult male and Tanner staging is simply a way of doing a physical exam and assessing this, in which you give a score for the genital development, for the pubic hair development and axillary hair development and it helps you place the child in those previous growth curves.

Then you can do the same for girls. In that case you are assessing breast development, public hair development and axillary hair development. And, again, you can see that girls at a given age during the junior high, high school age can be extremely varied in their place on the pubertal growth curve.

So, the other way of trying to approach this in terms of a study to document where your patients were at is to do hormonal measurements and I am not going to go into that in detail. Dr. Levine may go into it some more, but just to say that there is variability in terms of testosterone levels or estradiol levels or gonadotrophin levels, whatever you want to measure.

So that at least from my point of view, and my colleagues can argue with me, there is no one gold standard hormone or set of hormones that you can measure that will really put your child into the growth curve position in terms of puberty any better probably than Tanner staging.

So, let's go into growth charts and standards some more. Now, the one that is most familiar are the growth charts for height. This, I am afraid, doesn't project terribly well, but this is -- the blue is for boys and the pink is for girls. We will take comments about whether this is sexist or not at the end of the question and answer period.

Basically, what has been -- and this happens to be from the national database of children from a statistical sample of the United States in the late seventies and early eighties and what is done is that you go out and you try to find a representative population and we will come back to that point. You measure everybody's height and weight and then you do your statistical magic and you end up with a normal range, which is shown here in white, plus or minus two standard deviations, these particular charts are 95th, a 5th percentile. Then that allows you to do two things.

One is you can sort of place the child in terms of how does he or she compare to their colleagues and, number two, very importantly, with longitudinal observations, you

you have to understand age and sex-related standards to what standard group. Again, this is reasonably well-defined, but, you know, there are big differences that can appear.

There are differences in ethnic groups and, again, this is well-documented by a number of studies. So, depending upon your racial origin, your country of origin, you know, even where you live within the United States, there are small differences so that either you have a large enough group so that by pooling the data, it essentially is the same kind of representative group as was picked for the U.S. Health Survey, or if you have a preponderance of one ethnic group, you might think about using specific ethnic group standards.

Also, to mention another potential problem is that there is a secular trend. Now, this is certainly over the last century or so, there is no question but what males and females in our society as adults are taller than they used to be. This is the so-called secular trend.

Now, most of the data in the United States says that the secular trend is slowing down, that, in fact, over the last 10 to 20 years that probably there hasn't been a real shift in growth rates, growth charts, but that is still argued about. And then to take -- as you get out to countries beyond the United States, a rather amazing phenomena has been seen. The increase in height of adult

males in Japan, for instance, has increased by six to eight inches since World War II, presumably as a result of change in early infant feeding practices. But all you have to do is to ride on a Japanese subway and you can see that the younger men tower over the older men considerably.

Of course, if you are traveling with my wife, she towers over them, too. So, she was always easy to identify.

so, let's then look at an important issue here that we are going to, I am sure, spend more time on later on in the conference, which is catch up. Now , this slide really just sort of defines what catch up growth is and the model here was, in fact, malnutrition. so, this was an experimental study.

So, here is what might be called the expected growth curve. If you become hypocaloric or are made to be hypocaloric, you can see that there is essentially a flat line here for as long as you maintain the hypocaloric intake and then at the end of that when you start to refeed, you will, in fact, get more rapid growth than usual, remarkably, over and over again, back right where you would have been if you hadn't had this insult.

Now , this has been documented time and time again in animal studies and in human studies but it is not always perfect. This is just an illustration of a child who had recurring problems of not eating well and you can see the

differences in the growth chart. You can see here that the height is falling off. So, it is, you know, changing percentiles .

Then after the end of the second insult, it actually resumes this growth up to about the 50th percentile. And if you look on the growth rate curves, it is even more remarkable as to how well is correlated the various episodes there with even some element of overgrowth, if you want to call it that, that, in fact, leads to catch up .

Now , there are, in fact, a number of influences that are well-known on the degree that you see as catch up. First of all, younger is better in terms of catch up growth. That is, you know, children under the ages of five or six, who have a short term insult, whether it is a disease process or malnutrition, will show catch up much better than somebody that is somewhat older than that.

Hormonal status is an obvious one. If you have a hormonal problem in the control of growth, you are not going to have adequate catch up growth. Then, finally, steroids have been well studied intermittently, mostly oral steroids and mostly higher doses than what most of us would use. But , nonetheless, there does appear to be a problem with the steroid treatment limiting the catch up growth. And that is an important issue.

Then I want to give a little bit about height prediction, which actually plays a role in some of the potential studies that might be done. The first thing, probably the most primitive method of height producing is to take your birth length and to correlate it with what the adult stature has done.

Now, these were not done as prospective studies but they have been done and the fact is there is a correlation but it is lousy. You know, it is down under .3, .2 for r squared. So, it doesn't explain very much of the variability. The mothers and fathers in the room may know the other rule of thumb, which is you double your child's height at two and that is going to be their adult height.

I won't bother spending much time saying that that doesn't always work, but this has been a -- some of the research to try to do better than that, there have been a number of ways to develop -- and I am going to cover two of them. First of all is mid-parental height. So, this is basically trying to say given -- since genetics is probably the most single important factor in height of adults, how do we say, well, we have got a couple that are of two different heights, two different height percentiles, how do we come up with an estimate as to how tall their children are going to be?

So, with girls, if you add the father's height and

the mother's height, you subtract 13 centimeters to adjust for the fact that males in our society are roughly 13 centimeters taller than females on the average. Or in boys you add that 13 centimeters to do the same adjustment and divide by two. That actually gives you a height in centimeters, which is the center point of if they had a hundred children together, what would the height be.

Now, this is an unlikely event. This, obviously, gives you a mean figure that you are never going to achieve in rational size families. So that you have to go through and make an adjustment for what range do you think will be reasonable and what people have settled on, I think, actually for convenience is that it is plus or minus 1.88 standard deviation. SO, about, you know, 90, 95 percent of the results would go within that and that -- since the standard deviation is about 5 centimeters, that means that about 8 1/2 or many of us use 9 centimeters, plus or minus a mid-parental target range, is what you would expect.

Now, the problem with this is, of course, that this is good for group data but it doesn't really tell you all that much about an individual child. In order to try to get at that people have, in fact, gone over to using bone age and bone maturity predictions.

This is just to illustrate the fact that during development there is a whole series of events that happen in

the bones that are seen in the hand and the wrist. And by using those and comparing them to standards that are now 50 years old and older, one can come up with an idea of how mature the bones are and then you can say, oh, yes, the average child who had a bone age of let's say eight years had achieved a specific percentage of their height and you can come up with another estimate.

Now, this is a lot better than measuring birth length, but it still is somewhat chancy for the individual patient and I think most of the pediatric endocrinologists in the room use it like I do to reassure those, if you can reassure and not talk about it in those that it looks like it is not so good.

So, then finally, before getting off the podium, I just want to mention the hormonal influences and some markers of growth. There are multiple controlling growth, as we saw at the beginning of the slide; genetics, nutrition and general health are probably all crucial in. their influence on growth. There are a variety of hormones that we brush by and Dr. Levine will go into some growth hormone, IgF, thyroid, sex hormones, steroids, all of which play a very extremely important role in the control of growth and any influence of those can have a problem.

so, in conclusion, what I have tried to do in this half hour is to just go through the general as:pects of

growth and development in children.

Thank you very much.

I will get Dr. Levine's first slide for her.

[Applause.]

DR. LI: Thank you very much, Professor Hintz, for that very clear discussion on growth and development. Thank you also for keeping us on schedule.

Our next speaker is Dr. Leonore Levine and Dr. Levine will speak on HPA axis assessment in children.

Dr. Levine.

Agenda Item: HPA Axis Assessment in Children: Advantages and Limitations

DR. LEVINE: Thank you.

Maintenance of the normal hypothalamic pituitary adrenal axis is important for normal glycemia, for normal tension, for general well-being and our response to stress. This is a schematic outline of the hypothalamic pituitary adrenal axis. The hypothalamus releases corticotropin-releasing hormone and arginine vasopressin in response to the input of a number of neuromodulators. This results in the secretion of ACTH by the pituitary. ACTH then stimulates the release of cortisol by the adrenal gland.

There is a feedback system whereby cortisol will feedback in a negative feedback manner on both the pituitary and the hypothalamus to suppress the secretion of

corticotropin-releasing hormone and ACTH. There is a short feedback loop of ACTH on the hypothalamus and actually an ultra short feedback loop of corticotropin-releasing hormone on the hypothalamus.

Now, ACTH is secreted in a pulsatile manner in a circadian rhythm and this is just a slide showing you the higher levels of ACTH in the early morning, the decrease in ACTH secretion throughout the day with the lowest levels late in the evening and then the early morning rise again in ACTH, with the peak achieved in the early morning.

Cortisol is also secreted in a pulsatile manner and, again, with the same circadian rhythm; again, the highest levels occurring early in the morning and then decrease during the day, although with continued pulses, with the lowest levels reached shortly after the onset of sleep and then the beginning rise again in the early morning.

The peak cortisol level is achieved between 5 o'clock and about 9 o'clock in the morning with inter-individual variation, although the pattern within one person is generally quite consistent and this just shows you the pattern of cortisol secretion in someone studied over four days. And, again, you can see that the pattern was very similar throughout those four days.

Now, there are a number of tests that we use to

evaluate the hypothalamic pituitary adrenal axis. There are those which evaluate the basal adrenal activity and those which are the dynamic tests of the hypothalamic pituitary adrenal **axis.**

Morning cortisol, either plasma or serum, is a very simple measure. It requires just one blood drawing. However, because of the variation in the time of the peak, we may miss that peak serum cortisol. Twenty-four hour integrated cortisol gives us certainly a better evaluation of the cortisol secretion pattern. However, it requires multiple blood drawing and hospitalization during the day and night to do these blood samplings.

Nocturnal integrated plasma cortisol, again, requires multiple blood sampling and at least an overnight hospital admission. The 24 hour urinary pre-cortisol requires the collection of urine, 24 hour urine, in children, which can be problematic, and if done in an outpatient setting, there is always the difficulty as far as whether this collection is complete.

An overnight urinary-free cortisol also requires compliance of the patient. In addition, when urinary-free cortisol is suppressed, this measure may be less accurate. Urinary-free cortisol is very useful in the evaluation of Cushing's syndrome but may be less helpful when we are looking for adrenal insufficiency.

There are a number of dynamic tests of hypothalamic pituitary adrenal axis. The gold standard is the insulin tolerance where insulin is infused to produce a hypoglycemia. There are then multiple samples, which are taken and the rise in cortisol is measured. The metyrapone test, there is a standard test, which requires between four and six or seven doses with both blood sampling and urine collection and this requires a hospital admission.

There is a short metyrapone test where just one dose is given at midnight and a blood is collected the following morning. The standard ACTH stimulation test has been very widely used. The standard test uses 250 micrograms of synthetic ACTH. There is now interest in using the low dose ACTH stimulation test, .5 to 1 micrograms .

The corticotropin-releasing hormone test is a relatively newer test. This also requires multiple blood sampling and can be an expensive test. The insulin tolerance test has an inherent risk and there are certainly patients in whom this test is contraindicated. The metyrapone test can also produce signs of adrenal insufficiency and it also is sometimes poorly tolerated, causing nausea and vomiting.

Now , as I mentioned, the insulin tolerance test is considered the gold standard. Hypoglycemia is a very potent

stimulus for the release of the hypothalamic factors, which then result in increased ACTH and increased cortisol.

This is a test which simply illustrates it. This is the blood sugar in the top panel, which you can't completely see. A blood sugar falling to the level of 40 milligrams per deciliter is considered an adequate hypoglycemic stimulus for ACTH in cortisol release. And here you see the increase in ACTH and the increase in cortisol in individuals, who have normal function.

In those who have hypothalamic or pituitary deficiency, the rise in ACTH is inadequate and there is, thus, an inadequate rise in cortisol. The test was originally described using only cortisol measurements to determine whether or not the test was normal. However, there is recent evidence that patients may have an adequate response in cortisol and yet have an inadequate response in ACTH. So that if one only measures cortisol, one may miss a subtle deficiency in the hypothalamic pituitary.

This is just a slide showing maximum ACTH and cortisol and here is a group of patients, who had an inadequate rise in ACTH, but an adequate rise in cortisol. This is a slide, which shows the separation of patients, these having had an inadequate response to cortisol and these having an adequate response in cortisol to an insulin tolerance test and you can see that their urinary-free

cortisol levels were low in that group that did not respond.

However, you can see that there was marked overlap in these two groups. Some people have said that if you have a basal cortisol level of less than 17, then -- I am sorry -- this is all a basal cortisol -- if you have a basal cortisol level of less than 17, you will not respond adequately to stress and have a deficiency in the hypothalamic pituitary adrenal axis.

Metyrapone acts on the adrenal gland as an 11 beta hydroxylase blocker, resulting in a decrease in cortisol and then an increase in ACTH. And because of the 11 beta hydroxylase block, there is an increase in 11 deoxycortisol or Compound S. This test is illustrated here in comparison to the cortisol response to ACTH stimulation and in an insulin tolerance test.

I want to make sure I am saying the right thing. And here you see a group of patients who had an adequate response to the ACTH stimulation test, but an inadequate response to the metyrapone test, demonstrating a discrepancy between the ACTH stimulation test and the metyrapone test. Here is the same group of patients with -- compared their metyrapone response to an insulin tolerance test and here there was a better concordance between the insulin tolerance test and the metyrapone test.

Finally, the corticotropin-releasing hormone test

presumes that if when you give a bolus of corticotropin-releasing hormone, you get an adequate response in ACTH release and rise in cortisol, that that indicates normal hypothalamic pituitary adrenal function and that is that the pituitary and the adrenal are normally primed.

This is just an illustration of the corticotropin-releasing hormone test in our normal short children and, again, you can see the normal response in ACTH and cortisol in response to the infusion of corticotropin-releasing hormone. Most of the clinical studies have utilized ovine corticotropin-releasing hormone rather than the synthetic human. The response in ACTH is greater with the ovine of corticotropin-releasing hormone than with the human, although the peak cortisol level reached is similar.

The cortisol falls more quickly following the human corticotropin-releasing hormone. This just compares the cortisol level reached following an insulin tolerance test and a corticotropin-releasing hormone test. And as you can see, there is very good correlation in the cortisol response, which is achieved. There is much less correlation in the ACTH release.

I am sorry that this slide is on its side and actually I am not quite sure what I was going to use it for. so, I will go on. I was going to use it for the ACTH test.

Again, the ACTH stimulation test presumes that if

the adrenal response normally to ACTH infusion, then that adrenal glad has been normally primed and so the hypothalamic pituitary adrenal axis is normal. The standard test, as I said before, is 250 micrograms of ACTH, 1 to 24. More recently, there has been great interest in using a low dose .5 to 1 micrograms of ACTH.

This is a slide, again, which compares the response to a standard ACTH stimulation test to the response in insulin tolerance test, again, using the insulin tolerance test as the gold standard. And you can see that there is a very good correlation in the response of cortisol to these two tests. These were in patients post-pituitary surgery.

Both the IM and the IV ACTH test gives similar response. Again, this just compares the IM cortisol response to the IV cortisol response and you can see that the cortisol response is very similar.

There is also a very close correlation between the cortisol response at 30 minutes to that at 60 minutes following the standard ACTH stimulation test, although generally the peak response following the standard ACTH stimulation test is at 60 minutes, rather than at 30 minutes.

However, again, using the insulin tolerance test as the gold standard, there are problems with the ACTH test

and this just shows you again discrepancies in the response of patients with pituitary disease to the standard ACTH test compared with the insulin tolerance test and these are patients, who had an adequate response to ACTH, but an inadequate response to the insulin tolerance test, again, suggesting that they have a deficiency in the hypothalamic pituitary adrenal axis.

This is a slide, which again shows the same thing. These black dots are people who failed the insulin tolerance test. You can see that despite the fact that they failed the insulin tolerance test, they passed the standard ACTH test, again, showing the discrepancy between the responses that you may achieve with the standard ACTH test compared to the insulin tolerance test as the gold standard.

This is from a fairly recent paper in which Dickstein summarized the many studies, which have shown discrepant results with the standard ACTH test failing to diagnose hypothalamic pituitary adrenal deficiency, which was documented either with insulin tolerance tests or with metyrapone or with clinical presentation.

Dickstein recently pointed out how when we used the ACTH standard test, we achieved much, much higher doses of -- much, much higher levels of ACTH in the circulation compared to all of the other dynamic tests of adrenal function. Also, he pointed out how even with the low dose

ACTH stimulation test, we achieved much higher levels of ACTH in the circulation compared to the stressful situations that were depicted here, including cardiac arrest and resuscitation.

So, because of that and the data suggesting that the 250 microgram ACTH stimulation test may not be accurate' in diagnosing perhaps more subtle forms of adrenal insufficiency, there has now been a great interest in evaluating the low dose test. This just shows you the comparison of the low dose ACTH stimulation test to the standard dose utilizing 250 micrograms of ACTH.

This is cortisol, the 30 minute level following the low dose and the 250 microgram dose is not different. After that, with the low dose test, cortisol tends to fall; whereas, as I mentioned before, the 60 minute level following the standard test tends to be higher.

Dickstein also documented that although there were people who were using a low dose based upon body weight and adjusting it for body weight, that if you took very obese individuals and did a 1 microgram ACTH test, they responded as did normals. And, again, you can see that there is no difference in the 30 minute cortisol level following 250 micrograms versus 1 microgram of ACTH, 1 to 24.

This slide just shows how you may be able to document subtle deficiency in the hypothalamic pituitary

adrenal axis using the low dose test in patients with pituitary disease, who pass the standard test with 250 micrograms and even pass a test utilizing 5 micrograms of ACTH .

so, here are individuals, who have hypothalamic pituitary adrenal insufficiency, documented by the low dose test, but who would be missed by the 250 microgram test. This is just another slide, again, showing patients who have been on long term glucocorticoid therapy, who had responded normally to a 250 microgram ACTH stimulation test, but who had an inadequate response to the 1 microgram test.

Now, glucocorticoid treatment results in hypothalamic pituitary adrenal suppression by suppressing corticotropin-releasing hormone and arginine vasopressin secretion and synthesis resulting in decreased ACTH secretion and synthesis and decreased cortisol and finally adrenal atrophy.

The degree of the suppression of the HPA axis depends on the dose, the duration, the frequency, the time of day and the route of administration of the steroid.

Now , there have been a number of reports of the hypothalamic adrenal axis evaluation in patients receiving inhaled glucocorticoids and this is just one slide in which ten children with asthma on inhaled glucocorticoids were studied. Each one of these children had a suppression of

the nocturnal cortisol secretion as depicted in this slide.

So, overnight suppression of cortisol secretion was documented in these ten children and very interestingly all of these children responded normally to the standard 250 microgram ACTH stimulation test. Again, in this study, which was a crossover study using two different inhaled glucocorticoids, again, overnight suppression of nocturnal cortisol secretion was documented in all of these children over the two week period of administration of each one of these medications.

And a decrease in -- I think this is integrated concentration of cortisol, again, demonstrated in children on inhaled glucocorticoids compared to normal. This is an interesting study, where children obtained blood spot cortisol at home just before and after they inhaled their glucocorticoids . So, with a little lancet they put a blood spot on a filter paper specimen, which was then -- cortisol was then determined.

And all of these children showed a decrease in their plasma cortisol level during the day, which was significant one hour following taking the dose of inhaled steroids and in the midday just before lunch.

I believe this is -- and, again, this just demonstrates the decrease in urinary-free cortisol in patients on inhaled glucocorticoids, again, compared to

normal .

I think I am just going to skip this slide because it is somewhat repetitious.

There are many, many children who are treated with inhaled glucocorticoids. So, comparatively, there have been very few children who have been studied. However, certainly, suppression of the hypothalamic pituitary adrenal axis has been well-demonstrated in children and adults receiving inhaled glucocorticoids and using all of the barometers, which I have just reviewed.

Certainly, as I mentioned, many, many more children have been treated with glucocorticoids inhaled than have been studied. Of the studies, certainly, there are problems with a number of these. Many of these lacked a control population. Certainly, previous oral glucocorticoid therapy may confound the studies. Variable doses and duration of therapy have been utilized. Different inhalers have been used. Different tests have been used to assess the hypothalamic pituitary adrenal axis and different criteria are used to define what is normal and what is abnormal.

so, certainly there are a lot of problems with a number of these reports. So, finally, what is the most appropriate test to recess the hypothalamic pituitary axis and what is the clinical relevance of hypothalamic pituitary

adrenal axis suppression?

Certainly, any test, which is used in a large number of children has to be convenient. It really cannot, I think, involve multiple blood drawing. Certainly, it should optimally not involve hospitalization and to be as disruptive, as little disruptive as possible. Whether the low dose ACTH stimulation test will be the answer, I really can't say at this point, but certainly recent evidence suggests that the low dose ACTH stimulation test may be a very sensitive test. It is certainly relatively easy with that risk and can be performed in an outpatient setting.

Finally, what is the clinical relevance of HPA axis suppression? I think we really do not know the answer to this. I think we do not have sufficient evidence, sufficient information yet and certainly we are going to need a lot more long term follow-up.

There have been very few reports of symptomatic adrenal insufficiency in individuals treated with the inhaled glucocorticoids, but whether there are more subtle long term effects, I think we really don't know.

Thank you.

[Applause.]

DR. LI: Thank you very much, Dr. Levine, for that excellent presentation and thank you for bringing up the key issues right up. front and bringing up for our thoughts, at

least, the issue of clinical relevance

Just to keep on schedule and to remind ourselves of our schedule for this morning, we will have a question and answer period later this morning and our panelists will have the opportunity to ask questions of **all** the invited speakers and that will begin just before lunch after Dr. Hintz's second presentation.

Our next speaker is Dr. David Allen from the University of Wisconsin and the title of his lecture to us is "The Influence of Inhaled Corticosteroids on Growth. "

Dr. Allen.

Agenda **Item:** The Influence of Inhaled **Corticosteroids** on Growth: A Pediatric **Endocrinologist's** Perspective

DR. ALLEN: Thank you, Dr. Li.

I would just like to thank the committee for the opportunity to be here and participate in this very interesting and important meeting.

My task in this short time is to provide a sort of conceptual overview of the question about the effects of inhaled corticosteroids on growth. And as you can tell from my title, while I think we have learned about the answers to this question over particularly the last five to seven years, I think new questions continue to emerge and remain to be answered.

1 would like to touch on each of these following points in my presentation and begin by making a couple of comments that I think are particularly relevant to understanding the literature as it relates to growth and perhaps formulating new questions about the issue of clinical relevance.

As with any of the potential side effects that we are discussing when it comes to inhaled corticosteroids, the key issue is to try to distinguish between detectable physiologic perturbations, which give us an indication of the systemic presence of the inhaled corticosteroid, some of which may reach statistical significance and, therefore, be reportable as a positive finding in a study and separating those from what are really long term clinically relevant adverse effects.

When it comes to the issue of growth, this raises a couple of questions. We have already heard Dr. Jenkins call our attention to this sort of conventional, clinically relevant, long term effect in terms of growth suppression and that is the issue of reduced final adult height. But I would like to suggest to everybody here today that as we move the treatment, anti-inflammatory treatment of asthma toward children with milder degrees of disease, that we have to consider some other possible growth effects as perhaps clinically relevant to that individual and to their family,

such as short term growth suppression, which might result in shortened childhood stature.

Now why is it so appropriate to be concerned about the effects of corticosteroids on growth and particularly inhaled? Well, this is a slide that depicts a very complex interaction between glucocorticoids and the growth axis. This probably is more appropriate -- it says exogenous glucocorticoids over here but I would like to say that it might be more appropriate for you to think about this in terms of excess glucocorticoid effect.

One of the important concepts to keep in mind here is that excess glucocorticoid effect doesn't necessarily imply that the concentrations of glucocorticoid have to be higher than normal. An adverse effect on the growth axis could also occur if the presence of glucocorticoids are there at times that are inappropriate compared to normal.

For instance, you heard Dr. Levine mention that the cortisol axis is at its nadir right around the time that an individual goes to sleep and I don't believe that it is any coincidence that the growth axis is most active in the hours just after sleep when the cortisol axis is at its nadir.

Now, this slide summarizes a whole variety of in vivo and in vitro investigations, which show the multiple sites at which glucocorticoids interact with the growth

system. And I think you can summarize this by saying virtually every place you look in the growth axis there is antagonism between glucocorticoids and growth.

There is an enhancement of hypothalamic somatostatin(?) tone with glucocorticoid excess that disrupts pulsatile growth hormone secretion. There is inhibitory effects of glucocorticoids on the expression of the growth hormone receptor, in the binding ofgrowth hormone to its receptor. There is direct inhibition of the bioactivity of insulin-like growth factor, which is a second messenger for the growth hormone system.

There are potent effects on collagen synthesis, which are important components of linear growth and a final area, which has not been examined in as much detail as these others, but certainly is a conceivable area that could inhibit growth would be the inhibitory effects of exogenous glucocorticoids on the adrenal glands androgen production.

Now , when we talk about inhaled corticosteroids in contrast to oral dosage, where there is a fairly reliable connection between the dose administered and the dose experienced by the body, there are a number of factors that determine the extent to which the individual is exposed to the drug. I don't have to review that, I am sure for most of the people in this audience, but certainly what is delivered from the device has to undergo a lot of variables

in terms of technique and individual variations in determining the ultimate drug that is deposited in the airway.

There are important differences between the different preparations in terms of their potency, their binding affinity to the glucocorticoid receptor, the way they are metabolized to either inactive or more active metabolizes and how the body handles them and eventually excretes them, that also have important effects on the overall glucocorticoid effect experienced by the individual.

But, perhaps, what is not as well-known to this audience is some other factors that are related to the individual themselves or the child, him or herself, that might influence their particular sensitivity to the adverse effect of growth suppression.

The child's age is probably of importance. Dr. Hintz mentioned that there are certain critical transition points in normal childhood growth, where the body seems to be switching from one mode of growth to another. These are areas or times where some children experience profound slowdown in the growth and, in particular, the immediate prepubertal years. That might be an important time when the effects of these steroids might be more pronounced on growth.

There" are certain families that have pronounced

exaggerations of slowdowns in these transitions; the growth pattern of constitutional growth delay where these individuals seem to have less resilience of their growth axis at certain times of life. They might also be susceptible, more susceptible to growth inhibition.

We have heard a lot about the severity of asthma as an additional component affecting growth and another very interesting area that we have little information about is whether the timing of administration of the glucocorticoid is a critical factor. One could imagine that administration of glucocorticoid at night in a prepubertal child when the growth hormone axis is usually the most active might have a disproportionate effect on growth compared to, say, administration earlier in the day.

Now, confounding the studies of the effects of drugs in inhaled corticosteroids on growth is the underlying effect of asthma itself on growth. This is an older slide from 1981 indicating that if you look at a population of children with asthma, and I would imagine, although I don't know for sure, that this is a population of children with at least moderate asthma, given the date of this study, that we see their heights are relatively comparable to individuals prepubertally, but that during puberty, this height decrement develops indicating that there is a delay in the growth and development axis of individuals with asthma.

This would be a typical response to a long term chronic illness in any individual, but that eventually with resumption of growth as the puberty finally ensues, there is attainment of normal adult height. So, I think this slide makes a couple of important points that have actually been validated by recent studies and that is that while this effect of asthma and particularly moderate to severe asthma can't be ignored. I don't think that we should exaggerate it as well.

The studies that I will be referring to and I think most of the speakers this afternoon will also refer to indicate that when you look at the prepubertal childhood population, the heights of those individuals and the bone ages of those individuals are not substantially impaired. so, it doesn't look like in the populations being studied in most of our current studies that mild to moderate asthma is having a substantial effect itself on the growth of these individuals, at least prior to puberty.

Let me briefly review the studies of inhaled beclomethasone on growth. I would like to preface this by saying in the last six or eight years there has been a marked improvement in study design of this issue and I think the studies that were done prior to that time can largely be ignored because they had poor controls and they were largely observational . And we know from studies of compliance in

asthma populations that even patients that we considered exhibiting good compliance are taking their inhaled corticosteroids probably 60, maybe 70 percent of the time.

So, older studies that were observational probably, number one, don't realistically lock at the dosages that they describe that they are looking at and also probably demonstrate that in real life, at least with the older approaches to asthma therapy that most people protected themselves from any adverse effects of inhaled corticosteroids by titrating their inhaled corticosteroid use to symptoms and demonstrating the usual degree of non-compliance .

Now , one way of looking at this, as I mentioned earlier, is just to look at the final adult heights of individuals that used inhaled corticosteroids for asthma. This is a study from the Mayo Clinic group that was published in 1997, looking at their experience of final heights and the yellow dots here are the individuals who have been treated with inhaled corticosteroids only during childhood and this was basically comparing them to, again, this one way of looking at expected final height, the mid-parental height.

You can see that the individuals fall along the line of expected mid-parental height and you probably can't see these purple dots on the background; other asthmatic

individuals, who did not receive steroids.

Now, there is one other study from the 1980s that gives this kind of data but those are really the only two studies that we have available and this n here is 17 individuals. So, our conclusions, our present conclusions, about the fact that the final adult heights of these individuals seem to be normal is based on very few data points. But what we have is quite reassuring.

At the other extreme, we have the ultra short term analysis of knemometry, which Dr. Hintz described briefly, and I am not going to spend much time talking about this, but I did want to call to your attention the fact that if we look at the predictive value of knemometry in the prediction of long term total statural growth, until we get out to about a hundred days of analysis of knemometry, we are nowhere close to having a reasonable estimate of long term total body growth.

You can see the usual duration of most stadiometry studies has been around here six weeks or so in duration and the range of accuracy in terms of predicting the correlation with the annual growth over the next year is in the range of a hundred percent error on either direction.

so, if we look at the different studies that analyze growth, we can group them roughly into short term studies, such as knemometry and many of which look at bone

markers, what I call intermediate term studies, which are in the range of an annual growth evaluation of 12 months and the long term study of long term stadiometry, say, for instance, greater than three years or actual final adult height analysis.

The point of this slide is to emphasize that if our clinically relevant adverse effect is changes in height, whether it be childhood or adult, that we require longer term studies to really get valuable information from that. Now, one of the problems of moving from the intermediate term to the longer term study, of course, is consistency of drug administration and avoidance of a lot of drop out of patients.

I think that is why today the most valuable information that we have to date about this issue comes from intermediate studies of about 12 months duration where the compliance with taking the medication can be reliably monitored and the patient groups can be held together with some confidence.

I will show you some data, which I am sure most of you are familiar with but just to make the point about beclomethasone and the influence of the prospective, well-controlled study designs that they have had on this question, here is the data from Duell(?) and their group in England,. looking at beclomethasone, administered 400

micrograms per day, without fail, day in and day out, to a population of children with mild asthma because a placebo -- the control group here is treated with placebo. So, obviously, this is a mildly affected group and what they showed was over seven months of treatment, there was a clear decline in the height, the growth achieved by the beclomethasone group; in this case, about 1 centimeter different.

They discontinued beclomethasone at that point, went to other forms of asthma treatment. They showed resumption of normal growth velocity but did not see catch up growth over that short ascertainment time.

A more recent study that was published last summer from The Netherlands compared the effect of 400 micrograms a day of beclomethasone with a long acting beta agonist. The way this data is demonstrated is looking at the change in the height SDS score. So, a child who is continuing to grow along his or her original percentile line would have a change of zero on this -- the way this is depicted.

You can see over the course of the 54 weeks there was a decline in the position on the growth curve of the children treated with the beclomethasone compared to no change in the Salmeterol-treated group.

The quality of asthma control on the other hand was better in the beclomethasone group than in the

salmeterol group, posing the difficult question about the double-edged sword of inhaled corticosteroid treatment.

Here is a summary slide that describes the results of four studies now in the past seven years or so that have described the growth effects of daily administration of 400 micrograms of beclomethasone to children with mild to moderate asthma.

The Tinkleman Study of 1993 showed a decline, average decline, of 1.5 centimeters, compared to theophylline-treated controls. This study raised a couple of, I think, very interesting questions that have come up in subsequent studies as well. One, the effect was more pronounced in the males than it was in the females. In fact, the female growth data did not statistical significance if it was looked at by itself.

Also, the alternative treatment group grew faster than was expected and tended to exaggerate the growth deficit experience by the beclomethasone-treated group. I have already showed you the Duell Study from 1995. Again, the pattern that appears interesting here is when this growth deficit is extrapolated over a year's time, we see a very similar affect on growth to the prior Tinkleman Study.

This was the first really well-designed study in terms of segregating out pubertal versus prepubertal individuals to avoid any contamination of growth

acceleration during early puberty.

The Dutch study, again, remarkably consistent findings in terms of the lack of growth and a more recent study in The New England Journal, and perhaps the most study, this might be 1998, I think, I maybe should say, again, 1.44 centimeters, a very similar type of study design.

so, the four studies that have recently looked at this have all shown very similar results.

so, the question is we have something that is statistically significant when it comes to beclomethasone and growth, what is the clinical relevance of this effect? And I have put together three possible examples because we really don't know the long term clinical effect, clinical relevance of this effect.

There is some information that suggests that the growth suppressive effects of the glucocorticoids are most pronounced in the early days of exposure, during the first six months or so of exposure, and that the child might recover or start to overcome the growth suppression by the glucocorticoids. If that is the case, you know, we might see this small degree of growth suppression over the first year or two and then resumption of normal growth here with some delay in the bone age from this early growth suppression so that the predicted final adult height would

be normal.

That is one possible outcome. Here is another possible outcome. Sometimes I get the question about, well, a centimeter a year doesn't sound like very much in the way of growth suppression, but if we think about that as a percentage of a child's normal growth, it is about a 20 percent reduction in the growth rate.

This graph shows the effect of that growth suppression over time. If that were to continue year after year, we would have some very clear proximal percentiles and- 1 don't think that it is hard to imagine that any of our children's parents would be concerned about that and consider that a clinically-relevant effect regardless of what the effect is going to be out here in adulthood.

Finally, if that does happen, what are the two eventual outcomes? Well, one outcome is that around the time of puberty with the greater resiliency of the growth axis, the growth suppression may no longer be a factor. Growth would again resume and with the delay in bone age that developed back here with early exposure, there is a greater time for growth and perhaps attainment of normal adult height.

On the other hand, if growth suppression does continue during puberty at the time when the sex hormones can themselves mature the bones and limit the time available

for growth, we might get some effects on final adult height. so, the clinical relevance remains unknown, but those are some possibilities.

What is the underlying mechanism o:E this growth suppression? I guess the short answer to that question is I really don't think we know at this point. There have been a few studies looking at the growth hormone axis, which have not been able to show any significant perturbations. There is some information that indicates that markers of collagen turnover and synthesis are reduced by inhaled corticosteroids . There are now two studies out, one recently by Soren Pedersen and their group in Scandinavia, showing that at least in prepubertal individuals, the bone metabolism does not seem to be effective.

As I mentioned earlier, we really haven't addressed the issue of this possible mechanism. So, the current evidence, the only evidence that we have available right now points to end organ effects, but I am a little bit suspicious that we just haven't developed sensitive enough ways to look at all these other axes.

So, we have this discrepancy between older information that shows normal final adult height in individuals treated with inhaled corticosteroids and newer information that seems to suggest significant growth effect of beclomethasone. How do we explain this discrepancy?

1 think the consistency of the study findings really rules out the possibility that there is just a few outliers that are driving the data analysis. But some of these other concepts are very interesting to think about. One is that in contrast to older studies, where more severe children were the ones treated with inhaled corticosteroids, we now are treating milder disease.

And we know that the more healthier the lungs, the better the systemic absorption of the corticosteroid. So, is it possible that with milder disease, we are actually seeing increased systemic absorption of the inhaled steroid in growth effects where we didn't see them before.

Certainly, an important part of these new studies has been the consistency of drug administrat:ion, the fact that they are closely monitored and that with a reasonable degree of reliability are assessing the effects of uninterrupted daily administration of an inhaled corticosteroid.

Another issue, I think, that is relevant to these studies is that there was no effort to really back titrate the dose to the lowest effective dose. It is quite possible that these children, for instance, in the Duell Study with mild asthma could have done very well with 200 micrograms a day rather than 400 micrograms a day of beclomethasone. And without making an effort, we could be seeing just the

effects of relative overtreatment in some of these studies rather than an unavoidable effect of inhaled corticosteroid treatment.

This relates to a current, very topical issue in the allergy community now about whether the long term control of asthma ought to revolve more around controlling inflammation at the lung level to prevent any kind of fibrosis or whether we should continue to use sinthon(?) control as the primary determinant of our medications.

Finally, this question about whether this effect might be peculiar to beclomethasone or whether this is related to the whole class of inhaled corticosteroids, I am not going to say much about that issue, except to remind the audience that when we look at the pharrnacodynamics of inhaled corticosteroids, there are important differences between compounds that could theoretically lead to a differential effect on growth.

We know that some drugs have more efficient first path metabolism, for instance, through the liver so that less drug gets absorbed through that route into the systemic circulation and the drug effect is more effectively concentrated in the lung at the site of the disease.

So, what conclusions can we draw at this point about the effects of inhaled corticosteroids on growth? I think there is little doubt left at this time that

continuous, what I call standard dose beclomethasone -- and this is the dose of 400 micrograms per day -- can slow short intermediate term growth. I don't think there is really any question about that anymore.

However, the clinical, long term clinical relevance of that decreased annual growth rate remains uncertain. Some of that depends on how you define clinical relevance. Certainly, the final adult height issue is unresolved.

I do believe that the effect of each inhaled corticosteroid on growth needs to be analyzed independently because there are significant differences between the compounds. These drugs have been a tremendous therapeutic advance for children with asthma. The effects on growth pale when compared to the effects of even small doses of oral glucocorticoids. I think that is a very important message that needs to be continued to be communicated because even frequent bursts of oral glucocorticoids are likely to give a greater growth suppressing effect than inhaled corticosteroid treatment.

Finally, a very important part of this whole discussion about growth is that unlike the HPA axis, which is quite mysterious and insidious in terms of our ability to determine what is going on there, there is nothing mysterious about our ability to detect the possible adverse

effect of a child's growth.

When I give lectures to people who prescribe these compounds, I make the point that I think every child who is being treated with inhaled corticosteroids should have their growth monitored at three to four month intervals, particularly during the first year of treatment. And with good technique, as was pointed out by Dr. Hintz, again, a wall-mounted stadiometer, good positioning by the child, an experienced person doing the measurement, with this kind of approach, it is not difficult to detect the child who might be experiencing growth suppression of inhaled corticosteroids.

So, we come back to this question, do inhaled corticosteroids impair growth? Well, there is little question that they can. There is little question that inhaled corticosteroids are capable of suppressing growth. The degree to which they do, in my view, all depends on how they are prescribed.

I think it was Dr. Li, who mentioned earlier that really the focus of the meeting is on discussion of the safe use of inhaled corticosteroids and, again, the take-home messages might be described with these four lines.

One, that we don't want the message to go out that the growth effect of inhaled corticosteroids are comparable or somehow worse than oral glucocorticoids. If a child

needs anti-inflammatory treatment for their asthma, they are going to be much safer being treated with inhaled corticosteroids.

The corticosteroids vary substantially with their properties and, in particular, for prescribers, we need to disabuse the notion that these can be compared on a microgram per microgram basis or dosed on a microgram per microgram basis. Prescribers need to become very familiar with the relative potency of the drug that they are using, so that they know the microgram recommendations that they should be using and they can make efforts to titrate the dose back down to the lowest effective dose.

Finally, when it comes to the growth issue, monitoring, regular monitoring of these children's growth will almost certainly allow us to detect the people severely affected and also allow us to reassure families, who need this medication that they can be prescribed safely.

Thanks very much.

[Applause.]

DR. LI: Dr. Allen, thank you for setting the clinical issues out for us so very clearly.

It is now time for us to take a morning break and we will resume promptly at 10:30 to hear Dr. Shapiro.

[Brief recess.]

DR. LI: Right now, we are resuming our morning

session. We have two additional talks scheduled for us before lunch. And our next speaker would be Dr. Shapiro, who will be speaking on orally inhaled and intranasal corticosteroids in the management of pediatric and allergic rhinitis .

Dr. Shapiro, if you are ready, we would love to hear your remarks.

Agenda Item: Orally Inhaled and Intranasal Corticosteroids in the Management of Pediatric Asthma and Allergic Rhinitis

DR. SHAPIRO: I appreciate the invitation to be here and I would like to talk about the clinician and how clinicians deal with asthma and allergic rhi:nitis today and give a bit of an overview.

So, pediatric asthma and allergic rhinitis, a clinician's perspective. As you have heard today and I am sure you know from the past, asthma is a growing burden to society. It is interestingly skewed to be more of a burden to the lower socioeconomic groups, but certainly affects all levels of society. And you may have seen lots of graphs that look at rising curves for numbers of hospital visits, emergency room visits, millions of dollars spent in prescription drugs for children with asthma. And these are just more numbers along those lines.

I thought it would be interesting instead of

giving you the usual national numbers for me to take a shift and focus on what happens in my community. And the Seattle King County Department of Public Health has put out a recent publication looking at asthma, morbidity in our community. You see curves that are similar to what we have seen for other parts of the country.

In King County, the county that is the home of Seattle and the surrounding area, childhood hospitalization rates rose by 25 percent in the last decade or so and asthma was the leading -- the second leading cause of hospitalization in children in our community.

As you might have guessed, if you look at the rate of hospitalization by socioeconomic class, you see that the level of poverty is greater or the degree of poor people, number of poor people, is greater in the upper curve than it is in the lower curve. So that down here, less than 5 percent of the population is at the poverty level; up here, greater than 10 percent of the population is in the poverty level .

so, these local curves coincide fairly nicely with what one sees on a national level.

A number of initiatives have come out of the problem of asthma as a burden to society in terms of morbidity, mortality and cost. There are a number of outreach programs, case management programs, guidelines and

they do a number of things. They teach triggers of asthma, avoidance of environmental factors. There are people who are very interested in monitoring systems, the use of peak flow in the community is growing.

Management plans are getting to be more popular. The idea of patients having a daily management plan as being the right way to take care of asthma and that in addition to a management plan for daily use, there should be an action plan for times of difficulty.

These ideas are catching on and the idea of control of medications used on all the time basis is catching on in communities. So, action plans, use of oral corticosteroids early on for acute exacerbations and the importance of having the doctor involved quickly when things are going down hill, these concepts are getting out into communities to a greater extent than in the past.

A lot of this is related to guidelines, such as the National Heart, Lung and Blood Institute guidelines and the 1997 Expert Panel Report 2, EPR2, that has been well-disseminated and continues to be disseminated in our communities to try to raise-the level of awareness about asthma.

Now, you have heard about the stepwise approach. Dr. Jenkins talked about that earlier today and I will just mention it again. And one way to sort out asthma severity

is to look at intermittent disease and then to look at mild, moderate and severe persistent disease. People who are interested in care of children with asthma usually accept that the persistent disease is inflammatory in nature to a significant extent and that in treating people with persistent disease, one has to be cognizant of inflammation and use anti-inflammatory medication, not a novel idea this morning. We have been talking about that over and over.

These guidelines, the EPR2, have sorted asthma medications into long term control, those controller medications, and then quick relief medications. Among these long term control medications, we have inhaled corticosteroids, non-steroidal inflammatories, like chromalin and nedachromil(?) and a number of other agents that can be used on an everyday maintenance program to decrease symptoms and to increase quality of life for people with asthma.

So, what does that mean for a child with asthma and how will a clinician deal with asthma of different severities? It is pretty simple. It is step 1. Quick release medication is usually simple beta agonist.

Once we get to step 2 and we accept that inflammation is an important issue here, we are dealing with long term control medication and the use of an anti-inflammatory. And as we get to step 3, we are dealing with

more and then step 4, more anti-inflammatory.

Let's focus in on what EPR2 tells us about the medications at each step and, again, Dr. Jenkins mentioned this a bit. At step 1, mild intermittent disease, no daily medication is needed. Step 2, the mild persistent, one daily medication, either low dose inhaled corticosteroid or chromalin or nedachromil and then other drugs may be options that are possible for this mild persistent sort of situation.

This is text that is adapted or adopted from EPR2. As we get to step 3, we have inhaled corticosteroid as being very, very important, either medium dose intranasal corticosteroid or low to medium dose inhaled corticosteroid with another agent. And as we get to step 4, we have high dose inhaled corticosteroid and other agents may also be used.

But for the moderate and the severe persistent asthmatic, the inhaled corticosteroid is on a special platform above other medications.

Now, the special benefits of chronic inhaled corticosteroids are reinforced by **a** number of different pieces of information that clinicians, who care for people with asthma are familiar with to some extent. There are a number of long term trials, mostly European, that speak to the benefits of long term, inhaled corticosteroid therapy.

And there are also pieces of information that" show an inverse relationship of inhaled corticosteroid use and asthma morbidity; for instance, hospitalization rates, so that you can look at the amount of hospitalization and see that the populations where there is most hospitalization usually has the least amount of chronic inhaled corticosteroid use.

And a few slides just to give you a glimpse of this sort of thing, a Dutch study looking at PD20, so airway hyperresponsiveness in children with asthma, showing less and less responsiveness indicated by higher I?D20 for children after months of inhaled corticosteroid versus no inhaled corticosteroid therapy.

Another slide from Soren Pedersen's group showing improved airway function after months of use of inhaled corticosteroid compared to a lesser degree o:E quality of lung function for patients who were not on inhaled corticosteroid. I know during the course of today, you will hear more about these studies and I just throw them up as examples of the sorts of long term data that American clinicians look toward when they make decisions about the use of inhaled corticosteroids in children.

These studies carry a lot of weight and make us feel that to do the best for our patients, inhaled corticosteroids are often the necessary, the best way to go.

This is from a study by Selruse(?) looking at early intervention with inhaled corticosteroid for patients who are newly diagnosed with asthma.

The important thing here is that in patients who have an onset of steroid therapy within months to a year or two of their diagnosis of asthma, there is an improvement in peak expiatory flow rate in this particular slide, that is much greater, much more significant than the improvements that one gets if patients have had asthma for years before they are started on inhaled corticosteroid therapy.

And this is a very important, almost moral, ethical dilemma or issue, at least, for clinicians taking care of people with inhaled corticosteroids. Certainly, when we are thinking about symptoms from day to day, we have options. We have options of just using bronchodilators and we have options of going the next step and using non-steroidal anti-inflammatories, chromalin and nedachromil.

We have newer somewhat anti-inflammatory agents, anti-leukotrine (?) modifiers that may well have anti-inflammatory potency. But we don't have any long term trials to suggest that the alternatives to inhaled corticosteroids will help us with long term issues, such as lung growth and airway remodeling.

Those of us who are concerned about not just symptom control day to day, but lung growth and what will be

the case for our patient in 10, 20 and SO years down the line walk around with heavy shoulders burdened by the issue of is inhaled corticosteroid the best thing for this patient and how do we tell a family about that, about how we want to control symptoms today and how we also want to make sure that we optimize lung growth and airway remodeling issues for that child for the future.

These long term studies make us feel very responsible when we are dealing with patients and the proper therapy for the young child with asthma.

This slide is from Pete Nagelston's work on asthma medication use in an inner city population and it speaks to the issue of the inverse relationship between asthma medication, inhaled corticosteroid use and anti-inflammatory use and morbidity. For this particular population, you see that a lot of people have beta adrenergic agent only. A lot of patients have theophylline and bet adrenergic agents and in this little pie-shaped area here you see oral corticosteroids and in this teeny, teeny little inhaled corticosteroid wedge, you see a 3 percent number.

so, this sort of confirms what others" have shown, too, that there is a lack of use of what may well be the best medications for decreasing inflammatory disease in populations that tend to have the most trouble in terms of morbidity and mortality.

The EPR2 is still a very current and certainly important guide for the treatment of asthma and the pediatric section has a tremendous amount to offer us today in 1998 and on to the future. The content, the pediatric content of EPR2 is being represented and showcased in a document that will soon be published and disseminated widely that will be called Pediatric Asthma: A Guide to Promoting Best Practice.

This document tries to deal a little bit more with how a pediatrician or a family practice person can easily, so to speak, treat asthma in his or her office in a user friendly sort of way. So, it is an attempt to have an even more user friendly version of the very important features or EPR2 .

In this guide that will soon be visible, there are sections on step down long term controller therapy. After starting long term controller therapy medication, regular follow-up visits, at least one to six month intervals are essential. And at those visits, you should monitor symptoms. You should monitor use of quick release medications. You should monitor pulmonary function, preferably with spirometry.

so, more concrete numbers than the general statement that you should follow up patients who are taking inhaled corticosteroids or patients who are taking regular

asthma therapy of any kind.

Well, how do you reduce this therapy? Getting a little bit more concrete, these guidelines talk about reduction based on evaluation of the child's severity and special considerations. Asthma can deteriorate at a highly variable rate. For inhaled corticosteroids some physicians suggest decreasing the dose by 25 percent every two to three months to the lowest possible dose to maintain control. This is very important, I believe, because there aren't many places where people talk about the importance of frequent visits and frequent step down.

Again, we heard about this earlier today but with the information that we have heard a bit about so far and that was in the briefing document and that we are going to be discussing in the next two days, some thrust towards getting very formal about frequent follow-up is going to be very important for the best care of asthma patients.

Areas of concern for me and for other clinicians taking care of kids with asthma, limited access to care can mean too little or too much medication. Limited access to care can mean living in an inner city center where culturally your family used to using medicine except on a crisis basis.

So, you don't get use of regular ongoing anti-inflammatory medication because it just isn't part of the

cultural milieu or limited access to care can mean being part of a middle class family, members of a health care organization where your visits to the doctor are very limited because if you are not really sick, you don't need to see anybody every one month or three months or maybe not even every six months because you are just not sick enough for that sort of thing.

So, you can be getting too little medication or you can be getting too much medication if you were put on a nice potent juicy, high potency inhaled corticosteroid after your hospital admission and you are not scheduled to see the doctor again for six months optimistically or 12 months perhaps more realistically.

Connected to that, visits for tapering not just crisis control are not part of the everyday lingo of pediatrics or primary care. They are for specialty care but we know that specialty care is not in the forefront today in terms of the way health care funding organizations, insurance organizations want to think about asthma management .

Another important issue that needs more attention from us is attaching growth charts to the care of patients with chronic asthma. This is something that specialists think about a lot. Pediatricians think about growth charts for regular well baby care, but that tapers off just as the

years of fulminant asthma difficulties or the possibilities of that are still very much before us.

So, the growth charts are perhaps not being kept with the sort of discipline that is important.

Now, it isn't all that easy just to do growth charts and that is another little glitch in the picture right now. Conventional growth charts may not give the information that more sophisticated Tanner adjusted growth charts can give. So, growth charts can end up being more confusion than help for certain situations.

This is a growth chart of a child who is in a long term clinical trial and the growth chart was a red flag in the trial because the child was falling off significantly in percentiles. This is a standard growth chart that one will see in a pediatrician's office.

This is just one example of correction of this patient's growth for Tanner stage shows that the patient is stable on the curve. So, even if you are doing growth charts, you can get confused by people falling off, who aren't really falling off. And this could be a negative reinforcement for use of growth in following patients with asthma. So, education is needed about how to adjust growth charts and not use just the typical everyday pediatric standard.

Let me move from asthma to allergic rhinitis and,

as we heard earlier, this is another inflammatory disease and you have probably seen slides on pathogenesis that show us that we start with sensitization and IgE antibodies attached to mass cells and allergen and IgE get together and we see mediator release from mass cells and sort of an early event, analogous to asthma and early phase reactivity.

We have influx of inflammatory cells and a late phase sort of reaction for rhinitis just as we have for asthma. We have millions and millions of dollars being spent in this country on allergic rhinitis just as for asthma also. This slide isn't particular to children. It talks about prescribed medications in general, ambulatory visits for congestion and not feeling well.

The highlighted here is the only one that is child specific, school associated loss in terms of indirect cost of rhinitis. So, just to show you that this is not just an adult disease and this is just one way of looking at the magnitude of dollars spent because of loss and morbidity from allergic rhinitis in kids.

We, of course, are talking about stuffy nose and not feeling well and fatigue and we think we are also talking about diseases that may be attached to having the normal flow and normal amount of edema disrupted in the upper airway so that otitis media, sinus disease may be secondary consequences in some people of allergic rhinitis.

Now, the therapeutic interventions that are used for allergic rhinitis are antihistamines, which are known to be best for itching and dripping of the nose and then decongestants that are often added to the armamentarium for the help of edema in allergic rhinitis. But it is the intranasal corticosteroid that seems to take care of the inflammatory situation. Again, we have the inhaled corticosteroid as the anti-inflammatory approach and with the anti-inflammatory agent, we are often able to see a decrease in itching and dripping and edema.

so, these drugs have become more and more favored by clinicians, pediatricians, family practice people, as well as specialists for the treatment of allergic rhinitis in even young children.

One slide just showing the comparison of improvements and symptoms with placebo compared with active treatment shown in a daily diary, so we see that sleep is improved. Daytime sleepiness, a trend of improvement and certainly stuffy noses improved by inhaled corticosteroid.

I have removed the trade names here. This is a comparison in kids of nasal corticosteroid versus antihistamine showing -- excuse me. I am not sure this is a pediatric study. It is a therapeutic comparison looking at nasal steroid versus antihistamine and showing that nose blockage during the day, at awakening, the amount of

sneezing, nasal itching, runny nose and eye irritation are improved significantly better with nasal steroid than with antihistamine .

so, clinicians are seeing that nasal steroid offers an option that is probably more potent for improvement in symptoms than antihistamine alone.

What about the cost? There is nothing cost-wise that would deter the clinician from turning to the more potent anti-inflammatory therapy for rhinitis. This is a comparison of several pharmacies in the Seattle area, two different long-acting relatively non-sedating antihistamines and three different nasal corticosteroids that are used in children.

You can see that the daily dose of these agents, a 30 day supply is about the same for antihistamine versus intranasal corticosteroid. so, clinicians are hearing more and more about rhinitis as an inflammatory disease analogous to asthma, the effectiveness of nasal steroid being more so than antihistamine and the cost being certainly similar to the antihistamine.

And patients also worry about systemic medication. They think that the antihistamine, the oral medication is the systemic medication and the intranasal steroid is not such a systemic medication.

Another thing about nasal steroids is that they

may well be disease modifiers as inhaled steroids for asthma are and this is just one of several studies that look at treatment in allergic rhinitis with intranasal corticosteroid in patients with asthma and effect on lower airway responsiveness.

In this particular trial, patients who received beclomethasone had an improvement in asthma symptoms, compared to patients who received placebo. This was intranasal use of beclomethasone compared to placebo, an improvement in asthma symptoms.

So, physicians are concerned and interested that judicious use of corticosteroids for asthma and rhinitis are safe. Are they safe? They are pretty convinced that they are effective and they are fairly convinced that these drugs are possibly disease modifying. I guess I shouldn't say fairly well convinced and then say possibly, but many clinicians that inhaled corticosteroids are disease modifying.

Today and tomorrow we are going to be talking about the problems with safety and how safety and effectiveness go together. I think after, again, reading the briefing document and hearing the initial comments today that we are going to walk away being much more cautious and much more judicious in the use of these agents. And, yet, a lot of us who are involved in the care of asthma and

rhinitis are worried about the media implications of this and that every time we make strides in education about the importance of anti-inflammatory medications, we meet with Time magazine, daily news type articles about diseases that are supposedly rampant among the patients who are receiving what we think might be the best medication for their asthma and allergic rhinitis.

So, while we want to be cautious and take the rest of the next two days to the level of optimal care for our patients, we don't want to lose progress that we have made in treating our patients in ways to alter the eventual disease outcome.

Thank you very much.

[Applause.]

DR. LI: Thank you very much, Dr. Shapiro, for that very excellent clinical summary. That makes us sure that all of us are starting with the same baseline information.

We return now to our friend and original speaker, Professor Hintz, who will now be talking on the issues and the design, the assessment and evaluation of growth studies.

So, Dr. Hintz.

Agenda Item: Issues in the Design and Conduct of Growth Studies: Population Studied, Duration, Methodologies of Growth Assessment, Statistical Considerations and Follow-

up

DR. HINTZ: First of all, I am going to warn you that this is not going to be a full lecture. What I hope to do is to bring up some points and get some discussion from members of the committees and audience. I have already warned Dr. Li that if he doesn't ask a good question, he can at least ask a question. And I encourage the rest of you to do the same.

Second of all, I think my qualifications for standing up here and giving this talk is that I have not only participated in bad clinical studies, I have actually designed them.

[Laughter.]

So, what I hope to do is to through an outline of some issues in growth studies and they start out with the population studied, duration of observations, methodology, follow-up and surrogate markers.

So, let's start with actually what is probably the most important of these, perhaps, is the population studied. so, as you have already seen from the previous talks, there are a lot of things that make choosing your population or at least defining it very important.

Age and sex we have hit over and over again. Ethnicity can play a role and the age of pubertal range, I guess, should be a better way to say that, is that whether

the patients are immediately prepubertal in what they may already be having a growth slowdown preparatory to the pubertal growth spurt or are they in puberty or in some studies, you can imagine that they are mostly through puberty and they are already slowing down in their growth again. So that I think those become crucial issues.

The exact disease state, medications and dosages are, obviously, crucial. I would guess that if you tried to pool a study of chronic asthma and nasal allergies together, that that wouldn't work very well, that you have to define the populations to be as similar as you can and ideally, you would have the other factors as similar as you can, balanced between the groups.

Medications and dosages are fairly obvious and then, perhaps, I even should have put this first and that is the issue of controls because how we interpret the data, whether it is a year from now or ten years from now or thirty years from now really relies upon the validity of the control groups shown.

Now, the easy way, and this comes back to studies I have not only conducted but designed, the easy way is to use historical controls. The tendency has been in pediatrics and pediatric endocrinology to say, oh, well, there is plenty of data about normal controls. So, therefore, we will compare it to, you know, the National

Health Survey data, the mid-eighties or late seventies or we will compare it to people that have come through our clinics in the past.

While that is easy, it always leaves you with a question. Was the composition of the group, the population studied, really comparable entirely to the historical control group. Without belaboring the point, I think we can all see in the literature and in our own experience cases where, in fact, that isn't true.

So, concurrent controls are the best if you can get them. I was actually pleased to see some of the studies that have been shown in this area and that I have read with interest the last once or so getting ready for this meeting is that, in fact, they did have a concurrent design. Obviously, you can't not treat people with severe disease, like severe asthma, but there are those studies that have already been discussed of mild asthma with and without placebo.

So, you know, the gold standard, so to speak, of the clinical trials industry is to have a placebo controlled, randomized double blind study. And then there are some things that modify that. Then in addition to that, when you are dealing with large numbers, I would guess that the audience out there from the pharmaceutical industry represent thousands of patients and that there is a point of

which having Phase 4 studies, even though they are not carefully controlled, have their uses in trying to find out how big a problem these things are. Certainly have been useful in the pediatric endocrinology business.

So then the issue comes up, well, how long are we going to do the studies. We have already talked about some of the problems with knemometry in which the correlation of the short term measurements with the longer term observations of actual height is not terribly good until you get out to the point where you essentially are at a half a year or beyond, as Dr. Allen showed.

On the other side of the stick, of course, is how long are the people involved in the study going to live. The ideal study that goes on 20 years, I think, is difficult to imagine, both on the basis of cost and on the basis of changes in personnel and people coming in and coming out of the study.

so, I think the point I wanted to make about control is that you need to have your control observations go on as long as your experimental observations are and that, by and large, in analyzing what questions are being asked here, as a first step, you would want to concentrate on what Dr. Allen defined as sort of intermediate length studies, something on the order of a year. Six months can be arguable, but a year is more or less standard. And that

at the longer length, what we are actually interested in is the final height or adult height of the children involved.

That, of course, you are looking at a study at a minimum of ten years. When we are designing our intermediate term studies, I think we have to keep in mind that at least there should be some follow-up to adult height . Again, these are difficult to do because, you know, patients wander off and in California, they not only change addresses, they change names and who is related to whom and everything else. So, it gets to be very difficult to follow up on the patient. But it is important to try to do so at least.

Also, in terms of final height, I think you cannot send out a post card in the year 2012 and ask people how tall they are. Pediatric endocrinologists have dealt with this issue for years. We always take a history of how tall the parents are when a child comes to us with a short stature. None of you will be surprised to know that husbands lie a lot about how tall they are.

[Laughter.]

Women get confused as to how tall they are and when you actually measure the height of parents, you get answers that are totally different. So, what I would extrapolate from that is that if you sent out a postcard and ask people how tall they are, you are not going to get good

data. You actually have to arrange a way of actually measuring them if you are going to have reliable observations .

But in terms of methodology, we have already talked about careful measurement of height and the need for something approaching a stadiometer. Now , this can be done in a pediatrician's office. There are a number of sort of simple devices not more expensive ones that we tend to use in which they are mounted on a wall. They work just as well as the others. You actually have to read -- you have to look at the ruler and read the number, rather than have a big display flashing at you, but they are perfectly adequate.

The big problem, of course, is what I stressed earlier about growth assessment. That is, you need a trained observer, who is going to be consistent in the way that they position the child. And that is actually a very -- not an easy thing to get. I don't know what the average turnover of office nurses is, but it is probably like one every year and a half or something like that.

Even in the academic environment, although I am on my second nurse, after 20 years at Stanford, but that is not the mean, that is an exceptional thing. So, a study can be done in offices, but you have to be sure to provide the right equipment and the right training.

Growth charts we have already talked about and the idea that when you are trying to pool data across years, you can use Z score analysis with the important exception that when you get out to the prairie pubertal range, then you can't just use Z scores based on age. You have to somehow take into account the child's puberty and it gets to become increasingly difficult to interpret the data when you are out in the peri-pubertal range.

so, the Tanner staging for pubertal development is first and then making predictions of final height, you know, again, if you can show that a certain treatment made a statistically significant impact on final height prediction, then that would, obviously, give you some information. It wouldn't be as great as having the concurrent controls, but at least it would give you some information.

Follow-up length of time, again, I guess I got ahead of myself, but you have to follow the patients long enough to answer the question that you are posing to the patient group. So, again, from my personal point of view, you know, at a minimum, you are talking about year long studies and even that at the end of a year long study, obviously, you can only conclude what is the influence of treatment X on a year's growth, not on whether that is going to translate into effect on the final stature.

We mentioned catch up earlier in the morning and a

couple of times and, again, under ideal circumstances those children may catch up once you are done with the treatment and you may not see a long term effect on the adult stature. You just might see some minor adjustment in the age of puberty. But you have to be specific about what question you are asking and what answer you can come up with.

Then, finally, the surrogate markers, we have already talked about mid-parental height and predicted adult height as ways of trying to assess in a group what their height outcome is likely to be. So, if you are dealing with a large enough group, then a mid-parental height score makes sense and people should be coming as a group within what is expected. Predicted adult height is somewhat better for the individual but for groups it is probably not much better in terms of what would you expect of the group to do.

But, again, they are sort of useful markers but no substitute for a controlled study. Then hormonal markers have been used both short term and long term. Having spent a good part of my scientific career in this business, I won't try to push that on you because I think the data shows that for growth studies, measuring these hormonal markers have been useful in the short term, you know, six months, one year outcome, but they have not been particularly useful in predicting the long range outcome in terms of heights.

so, I mention it only to tell you that I don't

think that that is the answer.

Okay. So now I am done and if there is nobody -- if there are no questions, I am in big trouble.

Agenda Item: Questions

DR. LI: Let me open the floor then to the committee and invite questions for Dr. Hintz. Actually, I will start with one, which is to -- if you wouldn't mind explaining how the predicted adult height is calculated and how it is actually predicted, based on what figures?

DR. HINTZ: The mid-parental height, I actually showed the equation for, which is basically the mean height of the parents for whether the child is male or female.

so, is the mid-parental height the same as the predicted adult height or is it different?

DR. HINTZ: There are other ways of predicting adult height. The bone age -- using the bone age is done in a different manner. If you remember the slide I showed of skeletal hands waving at you, there is a sequence of events from actually before birth on through the end of adolescence of the growth period in which there is an -- individual bones can be scored as to how mature they are and individual epiphyses and every one of our digits has epiphyses in it as well as the ristepiphyses(?) that show on the typical films. And, again, they have a known sequence of events so that you would basically look at a child's x-ray, compare it to some

standards and say, well, I know that his chronological age is 11, let's say, as an example, but his bone maturity looks more like an eight year old and, therefore, I would predict that this child is going to go into puberty late and end up, you know, whatever you predict.

And there are tables called the Bailey Penough(?) tables that most of us use and there are some other methods, too; Roche Tanner Teeson(?) and so forth, of basically taking the bone maturity and say this child has achieved a certain percentage of his adult stature and you can obviously measure what his stature is on the day you took the x-ray and then you do the manipulation with the percentage and you come out with an estimated -- and I underline "estimated" twice -- adult height, what you can expect for this child.

It helps to adjust for some of the inaccuracies of sort of the mid-parental height, where, obviously, any group of parents, any two parents, can have a variety of height youngsters and they are all within the range of possibility. so, the bone age is a way of trying to adjust for the fact that children mature at a different rate and they grow into puberty at a different rate and you come up with a figure of what you would expect.

Again, in terms of trying to imagine a study, you know, if you had data that showed that the patients did not

achieve by a significant degree their predicted adult height done either by the mid-parental height method of bone age method or both, then that would be a significant factor.

DR. LI: Thank you for that answer.

Other questions from the committee? We will start here. Dr. Gross.

DR. GROSS: Dr. Shapiro raised a point that either she or you may be able to answer for me. And that concerned the Tanner adjusted growth chart. Could either of you just briefly state maybe qualitatively how you make that Tanner adjustment? I didn't quite follow that in the. chart that was shown.

DR. SHAPIRO: Well, since I am not an endocrinologist, I just follow the chart and there are certain places where you find with a patient' s current Tanner stages and you plot -- the curve basically changes according to the Tanner stage. It is just a simple following a graph.

DR. GROSS: It is like a three-dimensional graph?

DR. SHAPIRO: No, it is a modified curve that has a dip in it that -- so the patients who are on Tanner Stage 1 are expected to be at a lesser level than patients who are in a more active growth phase. So, it is an adjusted curve, basically.

DR. HINTZ: It would be nice if it could be put in

3D because that is -- in essence you are taking, you know, a slice of time and projecting it forwards and backwards, depending upon how mature the child is. It is in essence similar to what we try to do with the bone age and height prediction is that you are using the, quotes, a real maturity, which is the hard concept to prove, of the child to adjust for whether he is going -- he or she is going to be maturing relatively early, relatively late, and that changes your prediction.

There are manipulations to try to do this but, of course, they all have their standard error.

DR. LI: Dr. Szefler first.

DR. SZEFLER: We have been focusing on steroids as medications that affect growth. In terms of study design, are there any other red flag medications that should be in the exclusion criteria or things to watch out for. And I am thinking of things like ritalin, which is a very prevalent use in pediatrics, periactin(?) . Are there medications that you can list in terms of study design to be watchful for.

DR. HINTZ: I think you have done a good job mentioning the psychotropic drugs, which, again, as endocrinologists we have a skewed view of. It seems like half the short population in California is on ritalin or something like that.

The other thing that is not that common, but the

thing to watch for is the thyroid hormone.

DR. SZEFLER: A second question I had in terms of that, because it seems like we are leaning to become knowledgeable in terms of growth velocity, in your present understanding of pediatric practice, what is the prevalence of the use of growth velocity curves? Is this something all pediatricians use, 5 percent of pediatricians use?

DR. HINTZ: Close to 5. You know, if you go into the pediatric endocrine clinics, you will find the charts have mostly been used. My impression in general pediatric practice -- and part of it has to do with the pattern of practice that I will come back to in a second -- it was mentioned by Dr. Shapiro, you know, that not everybody gets height measured every visit to a pediatrician.

This is a problem that pediatricians sort of -- and part of it is it is mandated now by the HMOs, they are taking new well child care and growth assessment in the first couple of years of life, but then they are forced more and more into an episodic care situation in which the mandate from the health care system right now is that if you are sick, you go see a doctor. If you are well, you don't.

And I think, therefore, we really don't get data. And this is insidious because, you know, if you have ever had your child into the emergency room, you know, what happens ordinarily is that they get a weight and then they

put the growth and that is true with doctors' offices, which you almost never get heights.

so, until we sort of get into a mode, I guess, of telling people and helping them to do it, such as allergists, such as people that are going to in the front lines in terms of looking for those problems, if you don't make the measurements, you don't have the data and it doesn't matter whether you have growth charts in the drawer or not because if you are not measuring height and you are not looking at growth rates, you are going to miss that.

DR. LI: Okay. We have a number of committee members who want to ask questions and I am going to go with Dr. Cara, then Dr. New, Dr. Baraniuk, Dr. Crim and Dr. Kelly in that order and Dr. Bone.

Dr. Cara, question or a comment?

DR. CARA : Actually I have a comment and it is related to this whole issue of adjusting for Tanner staging when you are evaluating a child's growth. And. maybe I can clarify some of the charting issues that you were questioning.

The bottom line is that the charts are simply different growth curves that take into consideration whether a child is an early developer or a late developer. Then it is up to the clinician to place the measurements that he or she obtains on the growth chart, depending on whether they

believe the child is an early or a late developer.

It doesn't take into consideration -- it doesn't make any calculation for you, in other words.

DR. LI: In other words, it is an educated guess.

DR. CARA: It is an educated guess, but first you have to determine whether that child is, in fact, an early or late developer. And the issue with steroids is that as we have talked or has been presented previously, steroids, obviously, can impair growth, but they tend to impair growth to the same extent that they delay maturation.

So that it can look like a child is a late developer, but that may simply be due to the fact that they are on steroids.

The issue is complicated further because when children have growth suppression during the peri-pubertal years for whatever the reason, once that suppression of growth is relieved, they tend to go through an accelerated puberty, resulting in early epiphysial closure and stunting of final adult height.

So that there are -- I guess what I am trying to highlight is the fact that there are some very critical issues around this whole Tanner staging and growth valuation process, especially during the teenage years and it is difficult sometimes to determine which is the chicken and which is the egg in terms of what is causing the actual

growth attenuation.

DR. LI: Thank you for those comments.

Dr. New.

DR. NEW: I have comments and questions first to Dr. Shapiro and then to Dr. Hintz.

Dr. Shapiro, I would like you to comment on whether a children who is suffering asthma without relief would have reduced food intake and, therefore, there is a factor of nutrition that might affect the growth. That is my first question.

DR. SHAPIRO: That is a very rare sort of scenario. In the urban or suburban setting, I really can't say I have seen that. I have seen one or two cases of people living in a much more rural, underdevel.oped sort of setting where there is an appearance of cachexia in a child who had use of accessory muscles and increased AP diameter of the chest and a great deal of wasting and it looked like there had been chronic obstruction to a fairly severe degree for years.

That, obviously, stays in my mind as being a very unusual example. Having said that, there was a recent article on food allergy and nutritional issues in kids who were put on restricted diets. I found that very interesting because there is a higher proportion of food allergy among more atopic asthmatics than there is among the typical

population. And it appears that there are children who were on diets without cow's milk and a variety of other foods, who may seem to be growing normally, unless you put them under a microscope a bit more. So, there may be more going on there than usually meets the eye.

But in general, I don't think nutritional deprivation is an issue with most of our kids with asthma.

DR. NEW: I wonder also then if you would just comment on the recent Environmental Protection Agency issues of particulate matters in the environment that are causing asthma to increase.

DR. SHAPIRO: That is a very controversial area. A lot of the most likely particulate materials are under the PM 2.5 level, which is, you know, kind of lower than where the EPA is focusing today. So, there certainly is data on with smoke and asthma exacerbations and there is interest in pollutant levels in general and asthma exacerbations. There are cities in the world that have been cleaned up environmentally where asthma has not improved so that it doesn't always work together.

There is a clinical trial now that is putting together data from long term growth in seven U.S. cities with kids with asthma and pollution standards in those cities. So, hopefully, in the future we will have more answers about that.

I would say it is very controversial and not clear.

DR. NEW: There was a paucity of data on whether there are environmental pollutions that are really causing this increased asthma frequency that --

DR. SHAPIRO: That is right.

DR. NEW: Ray, can I ask you questions because in general what we are concerned with is how tall you are going to be will depend on the rate of growth and the duration of growth. There are certain irrefutable facts, which is women are generally shorter than men and delayed adolescent patients tend to be shorter than early adolescent patients. so, the point that Jose made, which is that if you have a delayed adolescence, the very fact that your adolescent growth spurt is on a lower height makes you ultimately shorter.

In view of the fact that different pediatricians, who are treating children with asthma with inhalant steroids will be measuring their children in different ways and there are all these other variables, which you have mentioned. Do you think that there is a prayer that we will be able to distinguish 1.4 centimeters difference, which is what the clinically controlled studies have shown?

I mean, let's say we put out a thing and we say pediatricians of the world, you have to measure children

every time they come to you --

DR. HINTZ: I have already done that.'

DR. NEW: You did that.

DR. HINTZ: It didn't work.

DR. NEW: Okay. Well, that is what I wanted to know.

My final question is what is your conclusion about the previous historical studies of children given oral steroids either for asthma or for renal disease or other things?

DR. HINTZ: It makes them shorter.

DR. NEW: It makes them shorter.

DR. HINTZ: I mean, there is no question -- and I have forgotten whose slide it was -- I think it was David's, his take-home points -- oral steroids have a much bigger effect on growth than do inhaled steroids.

DR. NEW: But did they effect final height, David? I didn't get that.

DR. ALLEN: Two years ago we did a meta-analysis looking at history of steroid exposure, oral versus inhaled, and there was a clear association of the oral exposure with reduced height where that wasn't seen in the beclomethasone-treated kids.

DR. HINTZ: To go back to one of your questions, can you see statistically significance at a 1.4 centimeter,

the answer is “yes,” but it, obviously, has to be powered adequately statistically to do it and if you decide that you have to do it, you would try to keep the number of centers involved down to the minimum you could and make sure they all have the same equipment and the nurses or whoever are making the measurements will -- are trained and there is some sort of quality control.

So, yes, you can do that but the question that you could discuss perhaps later in here philosophically is does it matter, is a 1 centimeter difference in adult height a major thing for us to be concerned about or should we concentrate our efforts elsewhere?

DR. NEW: Thank you.

DR. LI: David.

DR. ALLEN: Could I add something to the answer?

I thought Maria’s question was referring more perhaps to the individual situation of a practitioner. We have already proven that we can detect **1.4** centimeters in studies, The issue is, you know, the doctor out there. I guess I would just add the relative importance of detecting the growth suppression is going to be proportionate to the degree of effect that you are seeing.

Now remember that the 1.4 centimeters per year is an average. Some kids are showing no growth suppression. Some kids are having a lot more. So, obviously, your

ability to detect it is going to be greater at an earlier stage in the children having a more profound effect. You know, in the kids that we really worry about that are having perhaps 2 centimeters, 2 1/2 centimeters change in the growth loss, I think that would be easily detectable.

DR. NEW: Just to answer, I agree with you that growth measurements are essential. I am concerned about whether you will have the sufficient precision in the end to make a judgment. I don't know.

I mean, we have got to remember that Tanner when he did his growth studies had one guy who did all the time for about 22 years and you see that --

DR. HINTZ: He was a British sergeant major --

DR. NEW: And Dr. Hintz here has had two nurses in 20 years doing it. Most of us are not that fortunate to have such devoted people.

DR. LI: Dr. Baraniuk.

DR. BARANIUK: I think implicit in this meeting is can we come up with some guidelines for the FDA and industry to consider for future prospective trials? In terms of enrolling patients, it seems like we have been bandying around the gone age, the Tanner adjusted age, the final heights. Does industry need to measure all of those in order to determine which is going to be the best measure?

Do we need to have a period with a pretrial growth

evaluation so that a change can be seen during a drug treatment period or with multiple doses? And should we always insist on including a catch up phase to -- or follow-up phase to determine catch up growth?

I was impressed in looking at the studies that the non-steroid treated groups often had an increase in growth relative to placebo controls. So, I would have to ask what should a control group be for the asthma treatment. Should we be banking 24 hour urines or plasma samples from the start and the end of studies so that as new markers appear in the future we can go back and evaluate those?

I think those may be useful recommendations.

And one other issue is what is the effect of exercise on growth? I got the impression from some of the Swedish studies that there was less of a steroid effect there compared to some of the American studies, where there seemed to be larger effects. I think we will discuss that more tomorrow, but in children who exercise more, do they have higher growth compared to other children?

DR. LI: I guess what I would say is that many of the issues that you have brought up, of course, are key issues and will be part of our detailed discussion tomorrow afternoon.

But I wonder, Dr. Hintz, if you had a comment about the question regarding exercise and growth?

DR. HINTZ: Exercise is well-known to be a stimulus of growth hormone, but there has never been a study that I know about that demonstrates that exercising children end up being taller children or not. Again, all the kinds of things that we have said already and we will say the rest of the day and a half ahead of us about difficulties of comparing groups and carrying out long term studies are certainly true in that situation, too. So, it is not clear.

In terms of the historical experience of what is the biggest influence on the outcome of growth in rats, in cattle, probably in monkeys and certainly in "humans, it appears that early infant nutrition and protein intake is probably the biggest single factor. But this group, you know, our -- Dr. Shapiro's practice in Seattle, are relatively comparable on that level.

I would like to comment on the issue about should we be telling the pharmaceutical agencies how to predict height and do they need bone ages and so forth. I think on a practical level, these studies are going to have to be done so that they start out at Dr. Allen's intermediate level and then carry on so that, in fact, a look at whether there is an influence on predicted adult height done by bone age, I think, is going to be very important in those intermediate studies..

Ultimately, it will drop out, I guess, other than

saying "yes, " they did achieve their bone age or they did not, but I think that is something that has to be done if you are going to have an early warning system.

The other thing, which you have nicely brought up, that gives me a chance to emphasize again, the catch up growth and I think that any study in this area that is done is going to have to have a catch up growth phase, a post-study phase, if you like, and ideally you would like to see, perhaps, a crossover or something like that so that the patients that were on treatment go back on placebo and maybe the controls go on to treatment, but to see the effect of catch up growth.

You know, it means less to the American public and to the pediatricians and allergists of the world if after two years everybody ends up at the same place, obviously, than if, as has been shown with steroids several times, you don't end up back in the same place because you don't have adequate catch up growth when you come off the steroids.

But all those studies were done with oral steroids, as I have tried to emphasize.

DR. LI: Thanks for that answer.

Dr. Crim, you are next.

DR. CRIM: I have two questions. One, I think, Dr. Hintz may be able to address and I think the other one maybe Dr. Allen can address.

In terms of study designs -- and it may come Up tomorrow -- looking at growth velocity -- this is directed to Dr. Hintz -- looking at growth velocity, if one conducted a study, let's say, in the prepubescent period, if you were looking at the growth velocity where you expect to see this decline before puberty, one question I have is how long should a run in period be that one can get an adequate number of data points to determine exactly what a person's actual growth velocity is so that you can follow that person during the treatment phase?

And then the second part of that question would be what would one do in the case of a person that -- a child who required, let's say, rescue steroids and how that would affect that whole analysis of data?

I ask that question because I think there are a couple of studies in the briefing document in which the subjects were allowed, let's say, rescue medication of oral steroids, if it was less than seven days, they could stay in the study, but if it was more than that, if they required multiple episodes of rescue oral steroids, they had to drop out. so, in other words, if they require any rescue oral steroids, that will automatically make them a dropout and, again, this whole issue about the duration of the run in period.

DR. HINTZ: I think most pediatric

endocrinologists would consider six months as a minimum run in period. Also, there is a strong seasonable variability in growth that has been shown actually more in the cold northeast than in California, but, nonetheless, it does happen. So, even with a six month study if it was during the winter or early spring, let's say, you might get a false rate, false idea of the growth.

In terms of the issue about medication, I think the allergists are aware of the problem and I suspect maybe Dr. Shapiro can back it up, is that you have to take something. Obviously, you don't want children in there that are on oral steroids all the time or going in and out of the hospital all the time, but I would suspect that if you limited it to people that never have used steroids before they started on medicine, that you wouldn't have very many patients and it would be hard to recruit for.

I doubt that there is any data at all as to whether it should be seven days or three days or eight days for that matter. I think it is just an arbitrary decision.

Leonore, what is the data in terms of suppression in terms of days of steroids?

DR. LEVINE: I think that is quite controversial actually and if certain factors are -- have the drugs administered, say, just once in the morning, et cetera. I think certainly several days are pretty safe. They are the

people who use the period of two weeks that you have to worry about.

DR. CRIM: I guess that at least the data seems to suggest, at least some of the analysis is that growth velocity may be affected, whereas, you may not see an effect on the HPA axis, then that is why I guess the question would be in terms of a study designing that is looking at gross velocity with a seven day burst of rescue medication screw up all subsequent data or at least for a particular period of time in terms of assessing the effects of inhaled corticosteroids or nasal on growth.

DR. HINTZ: There are some studies that alter short time periods, of looking at effects of growth of the tibia and fibula and steroids and as brief as one week of steroids can be shown to have an effect on looking at growth as seen by knemometry. Also, with those studies, which were done in Germany, they had a catch up growth in the succeeding two weeks. I think the more stringent you can be within being able to run a study, obviously the better.

DR. CRIM: The other question I have, which may be a little brief, directed to me, with Dr. Allen would be this whole issue about the effect of asthma on growth. And I was just wondering -- you mentioned the study by Silverstein in which there was no difference in mid-parental height and those asthmatics who use and inhaled corticosteroids versus

those who did not.

I guess my question would be has there been any data either with knemometry or stadiometers looking at comparing asthmatics who are not on inhaled corticosteroids or let's just say beta agonists versus control. to see if asthma in and of itself affects growth.

DR. ALLEN: I haven't seen any data about that. I think the comment that Jose made about the effect of asthma perhaps being exaggerated in those years right before puberty was also substantiated by the slide I showed. I think that is where a lot of the conventional wisdom about the effect of asthma on growth has come from, that there is a -- could be a fairly profound influence of, say, moderate asthma on making the transition from the prepubertal to the pubertal phase of growth and you get a delay in that onset of puberty and there is an acquired relative short stature during that time.

But other than those kinds of studies, I haven't seen compelling information, you know, that asthma itself in either the prepubertal population or the adult population has a significant effect on height at the time. And I think the recruitment of, you know, if you look at the baseline populations of the modern day studies, they tend to substantiate that the kids are not short statured and they don't have substantial bone age delay.

DR. LI: Dr. Cara wanted to comment, then we are going to go -- no.

Okay. We will go on with other questions. We have maybe a little less than 20 minutes left and we have a number of committee members with questions. So, we will try to get to them all if we can keep the questions and answers focused.

So, Dr. Kelly, did you have a question for either Dr. Hintz or one of the other speakers?

DR. KELLY: This is for Dr. Hintz.

One of my questions was answered about the baseline, but in terms of using growth velocity curves, I was interested in terms -- when we are looking at the data that we now have in front of us or were given to us, how consistent is an individual patient along a growth velocity curve. We have seen how on the standard growth curves how they can alter and change but if they are always on the third percentile in that flat portion of the growth velocity curve between six and puberty, are they always on the third percentile or do they jump around considerably?

DR. HINTZ: They jump around a little. If you compare the jumpiness, to coin a phrase, of the growth rate charts, as compared to growth charts, there is a lot more jumping, partly because, you know, it is an exaggerated scale and party because of the difficulties of these

measurements. You know, it is one thing to measure a child's height and to have it track, you know, the 10th percentile, let's say, plus or minus a little then. It is another thing to try to get growth rate data every three months that make sense.

I think in my own case, I use sort of the six month growth rate data as being reasonable and. I ignore anything shorter than that.

DR. KELLY: So, if we don't have baseline data for six months, can we use growth velocity curves to even look at whether or not a certain therapy is producing a suppression?

DR. HINTZ: I don't think so. I mean, obviously, you can always do -- like I said, I helped, not only participated in but designed bad studies. You, can always, you know, do something, but I think -- it is a difficult situation if you don't have growth rate run in and growth rate data.

DR. LI: Okay. Thank you .

Dr. Bone, next.

DR. BONE: Thank you. I have a question, a specific question for Dr. Hintz and then a little more general question that will probably be addressed to him and to Dr. Allen.

Dr. Hintz, did I understand that for the

prediction of the adult height, the variability was for two standard deviations with 9 centimeters or is that right? Or was that 1 -- that was two standard deviations.

so, that would be about 3 1/2 inches in final height, something like that. Does that then tell us a little bit of an answer to Dr. New's earlier question about what we could say in an individual about the difference between their attained height and what they might have attained without treatment? I mean, that sort of sounds like --

DR. HINTZ: This would be a good thing to get in grouping because, obviously, the standard -- it is the likelihood that it meaning is bigger when you have a bigger n. But in an individual patient, as all of us can testify, I think we can have large errors and it is not because you are not --

DR. BONE: It also seems from my experience as a clinician dealing with more -- sometimes adolescents and older adults but occasionally children, that parents of sick children are maybe concerned about big differences in height, not 1 or 2 centimeters in the long run, at least that is the impression I have.

I am having an interesting time trying to synthesize some of the information here and it is striking me more and more that trying to evaluate the clinical

significance of data even from a year is a little perilous. Perhaps you and Dr. Allen would comment on whether I understand this about right at the level of discussion we are talking about.

We are looking, it seems to me, at fairly subtle differences, at least over the observational period. The studies we saw were around a centimeter and a half, not quite, differences in groups. But this is confounded a little bit by the fact that the underlying disease may affect growth velocity and there is also an effect on maturation.

The effect on maturation is such that it might mitigate the effect of a decline in growth velocity on final adult height. But I think it was Dr. Cara that pointed out that the degree of mitigation may be less than it appears to be because the delay in delayed pubertal growth spurt is accompanied by a delayed but eventually accelerated maturation process so the epiphyseal quotient may occur in a hurry as well.

Do I have that about right?

DR. HINTZ: Yes, you have that about right. If yOU would like to become a pediatric endocrinologist --

DR. BONE: Thank you very much.

DR. HINTZ: The peak philosophy on the average in puberty is lower for the children that mature late than

those that mature early, as we said a couple of times. so, that is exactly the -- if you just use the bone age -- late maturity, particularly boys, you can predict that they get taller than they actually do. For girls it is only about a centimeter. Our predictions are inaccurate in those that mature late in life and giving steroids that will delay the maturation process of -- presumably almost never been studied, particularly in that group, that would happen in children --

DR. BONE: And we don't really have if I understand correctly an established way of making that second adjustment.

DR. HINTZ: There is an established way -- I would like to hear Maria's comments on it, which is that one of the things about the Bailey and Pinot tables that were set up on a study that was done mostly during the -- published in 1945 or 1946 -- is that there are three different charts for late maturers, early maturers and normal maturers.

To my knowledge, they have never really been validated fully.

Maria, do you want to comment?

DR. NEW: There was a recent paper by Phil Aron(?) in which he claimed that even children with advanced bone ages should have high predictions measured on the daily -- you know, taking the average. But we have just done this

with a group of patients, who tend to have advanced bone ages. So, it is children with congenital adrenal hyperplasia and we have found that the adjustment should be made using the advanced bone age table.

But when you look at the difference between the high prediction using the average and the advanced bone age tables, the difference is very small.

DR. CARA: The other issue is that when Bailey and Pinot developed these tables, they were looking at normal children that were either early developers or late developers. They weren't dealing really with situations like precocious puberty or asthma or things that tend to delay or accelerate puberty more from a disease standpoint.

DR. BONE : Then to summarize my question I guess I was trying to get at is would we be better informed with regard to how we are actually going to manage these children if we focused our attention on something -- on measures that were more directed at assessing the frequency with which children have very substantial reduction in their growth, almost looking more at a categorical analysis rather than looking at the means in these case? Is that a more informative kind of measurement, Dr. Allen and Dr. Hintz?

DR. ALLEN: That is certainly one way to look at the issue and I think some of the documents that we will be looking at later today, you know, show how your

interpretation of the data can vary, depending on the viewpoint that you take, whether or not we are trying to select out particularly susceptible individuals, who might have a much more significant effect on their growth. Because I think the comments we have been hearing in the last five minutes, I think, do make it clear that, you know, for any particular individual, you know, looking retrospectively for the vast majority of these kids who are maybe having a slight diminution in their growth, it is going to say whether there was a clinical effect on their final adult height.

We are not able to precisely predict what a person's height is going to be accurately enough to answer that question. So, I think we return to the issue of focusing on analysis of growth velocity over time and individuals getting these medications and, you know, the issue of monitoring them and selecting people that seem to be having an effect.

I mean, that is going to be the best, the only predictor of a significant effect and until we segregate out an adolescent population and look at them after prepubertal growth suppression, we are not going to be able to answer the eventual question about final adult height.

But that is why I hope that the discussion expands a bit beyond just this issue of final adult height because I

am not convinced that that is the only clinically relevant effect that we are dealing with in these mildly affected kids with asthma.

DR. HINTZ: In other words, if you are shown as a sixth grader, you are short as a sixth grader, right? People can be upset about their stature at any length and you can tell them all you want that when you are 20, it will be fine.

DR. ALLEN: The question is, you know, if you wonder what is the reason to be worried about final adult height, and, you know, there is a lot of interesting data out there about the effects of eight on success and what not in society, but nobody --

DR. HINTZ: How tall are you?

DR. ALLEN: Not tall enough. And I exercise, too.

But , you know, the interesting question is is that because you are short as an adult or is that because you were short when you were in seventh grade that you might have certain effects later on? That is why I don't think it is so clear cut that the only relevant issue is being short as an adult.

DR. LI: That is a good point, Dr. Allen.

I would like to move along. We have at least five other committee members or guests who have questions. I would like to have them all have an opportunity to ask their

questions of the speakers. I am certainly willing to go over five or ten minutes past the hour, but no longer than that .

I believe that DR. Malozowski does have a question or a comment.

DR. MALOZOWSKI: My comment is regarding the issue of bone age, high predictions, the high predictions of normal . There is no study looking at bone age prediction of patient that received steroids. Steroids do affect bone and this may be a confounding factor when you predict final height . Aside from the fact that the standard error usually in height variation is about 5 centimeters, that you can be 5 centimeters above or below.

Therefore, in this particular population, I think that it will be very interesting to collect the data but to make the assumption that somebody will have normal height or something like this based upon bone age, I think, is incorrect .

DR. LI: Dr. Hintz, would you like to comment briefly on that? Would you agree with that?

DR. HINTZ: I would agree.

DR. MALOZOWSKI: The other point, I think, it is very important to qualify the paper by Silverstein that Dr. Allen presented because from the initial 800 patients approximately that they contacted, they only studied 58

patients that received steroids. Okay? And a very important point in this particular paper in which the height was normal in the patient that received glucocorticosteroids that the mean age at first contact with corticosteroid was 12 1/2 years. Being say that and remembering the growth curves, we keep in mind that most of the girls already are at the growth deceleration stage at this point and I don't know really how much these drugs have an effect have on the growth rate of this particular population.

It is not the same as children that started therapy at age four, six, eight. We are looking at puberty and the other point is the dose exposure, although probably most of these patients received glucocorticoid steroids, the dose were quite modest. The median doses were quite modest.

DR. LI: Thank you for those comments.

We will move along next to Dr. Liu and then Dr. Osborne, Dr. Hirsch and Dr. Oppenheimer, in that order.

So, Dr. Liu.

DR. LIU: I hope this is a short question but one of the things that we might take some lessons from would be what is known about the effects of low doses of systemic corticosteroids. I have heard this sort of bantered around and it is certainly relevant to this discussion about the effect of inhaled steroids is what other guidelines do we have from the use of systemic steroids either in an asthma

population that takes them regularly or an asthma population that is classified as having greater disease severity so it would be presumed to be more on high doses of inhaled or systemic steroid medications, compared to some other control group.

I mean, how much is this effect well-documented for people that you would expect to have some sort of effect on?

DR. HINTZ: I will take a swing at that one or David can correct me.

The problem is similar to some of this data. That is, that the mean effect on growth rate is fairly well-documented and the dosage at which it happens, which is really not very much above physiologic 20 to 25 milligrams of hydrocortisone equivalent per meter squared per day, you know, can, in fact, influence growth. But there appears to be an individual susceptibility factor so that you can't just give an absolute bottom dose for every person and trust it. But it is well-documented.

DR. LIU: Does that extend to final adult height? Is that the endpoint that is being looked at here?

DR. HINTZ: No. Most of that data is growth rate data not adult height data. I don't know of any off hand.

DR. LI: Good question, Mark.

Dr. Osborne.

DR. OSBORNE: I have a question that is fairly vague. So, I apologize. I really want to know what is realistic. I am asking mostly Dr. Hintz, but I realize there are others here who are both practitioners and have done many research studies. So, this is a question which is what is realistic to ask a practitioner to do that we can advise from these meetings? What is realistic to ask industry to do? So, my questions are is it reasonable to ask practitioners to follow height every six months or every year using Tanner adjusted scales? Is that a feasible recommendation, number one?

Number two, is it feasible to ask industry to come up with the lowest effective dose at which there will be less than a centimeter per year growth velocity change, recognizing you are going to need at least 120 people per treatment arm and maybe higher, depending on the stage of the patients?

DR. LI: I think the second part of the question we will address tomorrow, but maybe Dr. Shapiro and Dr. Szefler, perhaps, can just briefly address the question of how practical it is for physicians or pediatricians, especially, to be following, you know, heights on a regular basis .

DR. SHAPIRO: I have given this a lot of thought since this meeting has been planned and I think that this is

sort of maybe a next wave of guideline type work, a new initiative in terms of a thrust towards pediatricians about the importance of inhaled corticosteroids still, you know, retaining that and focusing on the follow-up and importance of growth choice in a way that is impossible for insurance companies to wash their hands of the issue.

So, I think that it is a prime time for the Academy of Pediatrics to have a position statement that is published for the academies and associations that deal with specialty care to insist upon this. I think it is very doable and that it is now public policy, political sort of issue, if that is what this committee decides is important.

I think it can be done with the right political effort .

DR. LI: Would you care to comment, Dr. Szefler?

DR. SZEFLER: Two questions that came up in terms of practicality and, you know, I think there is one balance that we don't look at. Asthma control, I think, as Gail very nicely pointed out, the asthma specialists are kind of thinking on a different level than primary care. We are thinking in terms of future in terms of lung development and there really needs to be kind of in the future a different way of practicing that incorporates both linear growth in patients that are on steroids and also lung growth to look at the effective component of the disease management.

so, I think it is very important and that is why I asked the question before, how familiar pediatricians are with growth velocity curves. And I would venture a guess most of them are not. That is why we have to be very careful in the wording because if we suggest monitoring growth, it becomes kind of one of those hodgepodge terms that Dr. Jenkins mentioned that are used in the past.

If we are just saying "growth," then we have to have some kind of practice parameters on how to measure growth and it seems on a research basis, we are really talking growth velocity, but on a clinical basis, the most we can expect is growth, linear growth measurements. And I would ask the endocrinologists do they feel confident that just reinforcing what should be done, like Gail said, on a regular basis, measuring growth. Is that sufficient to really pick up some of the growth effects or will they just pick up very significant growth effects?

DR. HINTZ: I think, by and large, you are going to pick up the remainder effects, you know, the more sensitive youngster, whatever it is. But I think that we shouldn't be -- have some instincts that we ca:n change practice standards, we can make it part of the care of every child's chronic disease not -- you know, to come every six months and to be made to --

DR. SZEFLER: I guess what we are afraid of, and

probably Gail would agree with me, is that if we give a label on this drug and then say because you are using this drug, you have to follow growth more carefully, it puts a stigma on the drug and makes it an inconvenient drug to use because now it encumbers a different level of practice standards.

DR. HINTZ: I think the practice standards are beginning to change. The phraseology I used of like giving a child with a chronic illness -- that puts the onus on illness in general. That puts the onus on the pediatrician and allergist, but I think unless we can make that change and make it better, it is going to be a problem.

DR. LI: I am going to move along.

Dr. Hirsch, did you have a question?

DR. HIRSCH: Well, some of these things have been partly answered but let me just quickly give one or two impressions so that perhaps you can correct my own way of thinking about this.

First of all, I know the meeting is restricted to looking at growth and not other aspects of what may happen, but it just seems to me inevitably that a growth change, although not significant in itself -- I don't care whether -- not growing basketball teams or if someone is a centimeter taller or not, but the issue -- I wouldn't want to do anything to human beings that makes them, taller or

shorter or anything else because without full knowledge of what I have done, the potential for this being a surrogate for many other things that we don't understand looms heavily in my point of view.

The second point is as I looked at the data, which we were given in preparation for this meeting, I thought the evidence was a little stronger than you all have stated as to the suppression of growth by asthma in and of itself. If you look at some of the data, it seems that percentages of individuals who have achieved different percentiles of growth, when that method of calculation was used, that the asthmatics who were the placebo groups also were not growing just as well as you would want.

Now, that being the case -- and this is my last point -- 1 am surprised that what steroids don't do is make people grow faster because you would expect if the steroids were good for the disease, it would not only clear up all the preliminary things, but whatever else it is that asthma has done to suppress growth. So, this leads me to the point that there is a lot we don't understand about the disease and about just what the steroids are doing in the disease generally and without some more mechanistic understandings, one is loath to make one or another recommendation.

Just comments on that if you would.

DR. HINTZ: I respect your opinion.

DR. LI: Anything?

[There was no response.]

Thank you for that insightful comment.

Ms . Conner.

MS. CONNER: As my primary responsibility here is that of representing the consumer, I think it needs to be brought up that I think the latest estimate is that 85 percent of patients, which would also include children, with asthma are not treated by specialists. And they are not treated by necessarily pediatricians. They are family practice. They are general practitioners and we are talking about mandating height measurements and this type thing. We tried to mandate asthma guidelines and we know that 97 percent of that group threw those guidelines in the trash.

I think it is unrealistic and anything that we do -- we have had a hard enough time getting this particular group of practitioners to recognize and value the use of inhaled corticosteroids in the treatment of ast:hma in children. We don't really need to do anything that is going to frighten them or make them more hesitant to do this. And I think we need to look at the group that we are talking about that treats the majority of the children and not necessarily the majority of the mild children.

They have moderate and, unfortunately, they treat

severe children as well.

DR. HINTZ: I agree with what you say. It is really a medical political problem, but it is possible to influence practice guidelines. A number of institutions are busily trying to, you know, practice guidelines that they are going to use and go back for quality control. If yOU are not using adequate treatment for somebody with asthma, you have got to explain that and, obviously, other things.

SO, I think by way of the American Academy of Pediatrics, a statement about that and then that will trickle down to the HMOS and other practice groups. I think we can enforce it.

DR. LI: By way of summary, would it be correct to state that previously, Dr. Hintz, you recommended that taking inhaled or inhaled corticosteroids ought to have their height measured twice a year?

DR. HINTZ: That is correct.

DR. LI: Dr. Kreisberg, this would be the last question and response before our lunch break.

DR. KREISBERG: I would like to make a comment. I find this a very interesting intellectual discussion about how steroids might influence skeletal growth and, more importantly, how it might influence lung development. But looking at it from **a** patient's viewpoint, it really doesn't make any difference. Most of these patients have to take

their steroids and they don't take them intermittently. Many of these patients take them indefinitely.

As a parent of a child and a grandchild with asthma, I can tell you that I would be willing to accept the down side of these drugs for the benefits that accrue and that I can't imagine as a physician I would make a decision to reduce the dose or discontinue a drug simply because there was a slowing of the rate of skeletal development if the detrimental effect would be that there would be an exacerbation of their asthma.

so, I think it is very interesting, but the most important issue, I think, here that we are talking about is not how to monitor and detect the children that develop retardation of skeletal growth, is how to convince companies and physicians to find the lowest effective dose that will suppress the disease and have the least effect, maybe not no effect, but the least effect on skeletal development.

DR. LI: I would imagine that many if not most clinicians would agree with that comment.

It is now ten past the hour and we will resume at 1 o'clock. Mr. Madoo does have an announcement to make.

MR. MADOO: This relates to expediting our consumption of lunch and suppressing hunger. The policy of this hotel is apparently we can reserve a table. So, in deference to the committee, if the audience can stay

somewhat glued to their seat while the committee sprints down the hall, that would be advisable.

There are two restaurants and then for people who can't make it into the restaurants, there are box lunches that apparently the hotel has prepared. So, I apologize for any frantic-ness but it is all in the name of science.

[Whereupon, at 12:10 p.m., the meeting was recessed, to reconvene at 1:00 p.m., the same afternoon, Thursday, July 30, 1998.]

A F T E R N O O N S E S S I O N [1:00 p.m.]

DR. LI: Good afternoon, ladies and gentlemen, and welcome to our afternoon session of the Joint Pulmonary Allergy and Endocrine Metabolic Drug Advisory Committees.

I thought we just had a terrific educational morning and I thank all our invited speakers for presenting so thoroughly and so clearly. I believe we will have an equally interesting educational afternoon and we will start with the industry presentations and we will go ahead in alphabetical order, meaning Astra followed by Glaxo Wellcome, Rhone-Poulenc Rorer and then Schering.

We have on the agenda time for a 20 minute presentation for each of the sponsors followed by a ten minute question and answer period, at which time people at the table and committee members and guests can ask questions of the sponsors.

My role, again, asks that the speakers keep to the schedule, including the 20 minute time for presentation and a ten minute question and answer time. Again, I apologize if I have to cut anyone short.

so, our first speaker then will be from Astra and Dr. Unman will be giving the presentation.

So, Dr. Ullman.

Agenda Item: Industry Presentation -- Astra

DR. ULLMAN: Ladies and gentlemen, my names is

Anders Unman and I have a clinical background in respiratory medicine and clinical pharmacology and I am vice president of clinical research and development at Astra Draku(?) in Sweden, which is the research and development company responsible for the development of budesonide.

I want to start by thanking FDA for the invitation to give an overview of our experience and documentation regarding Budesonide and the potential for growth related effects in children. My presentation will contain some relevant new data that was not included in the FDA briefing material and which the agency has not had time to evaluate.

I would also like to state that Astra is in agreement with the Agency that in the labeling for inhaled and intranasal corticosteroids, there is a need for adequate information and precautionary statements regarding potential effect on growth. The current labeling for Budesonide products on the U.S. market include such information.

We recommend that dosing should be individually adjusted according to disease severity and that growth should be monitored in children, which also is in line with current national and international guidelines for asthma management, guidelines that recommend the step down approach to the **lower** dose while asthma control has been obtained.

Budesonide is available in two formulations on the Us. market today, pharmaco Turbuhaler, which is a dry

powder inhaler for treatment of asthma and Rhinocort nasal inhaler, which is a pressured measured dose inhaler for the treatment of seasonal and perennial rhinitis.

In addition, we have two new applications currently under review by FDA. These are our inhalation suspension for nebulization, Pulmicort Repulse and an aqueous formulation of intranasal Budesonide Rhinocort Aqua(?). Inhaled Budesonide, Pulmicort, even if relatively new on the U.S. market, was introduced to the first European market 17 years ago and is today approved in more than **60** countries worldwide.

The clinical documentation comprises more than 25 tarlson(?) subjects and the accumulated marketed experience to more than six billion treatment days. Intranasal Budesonide or Rhinocort was introduced 16 years ago and is approved in more than 50 countries. We have clinical documentation on more than 10,000 subjects and market experience corresponding to 1.6 billion treatment days.

Our current knowledge of the safety of Budesonide is based on prospective clinical trials and the vast postmarketing experience. With regard to growth, we have prospective data on growth in children with all our formulations and we have data on short term, long term and recently also on parental height in patients using inhaled Budesonide during a substantial part of that group period.

I will focus on the most recently performed group studies with inhaled Budesonide and, as I mentioned before, some of these data have just recently been submitted to FDA for review. I should also mention that there are retrospective studies published on growth and use of inhaled steroids in which Budesonide has been one of several steroids studied. As these studies are not Budesonide specific, I have not included them in my presentation.

Dr. Soren Pedersen's group in Kolding has conducted short term group studies with Budesonide, using knemometry as a surrogate marker and also studied long term growth using stadiometry. And a very important piece of information comes from one of these studies in which the correlation between the very short term growth by knemometry was compared -- was studied to the growth measured by stadiometry.

This study was a single center, one year, open label study in 47 children with persistent asthma. They were treated with Pulmicort Turbuhaler in a maiden dose of 380 microgram a day. The changing growth during run in to the first knemometry during inhaled Budesonide treatment was compared with one year growth velocity obtained from the study of metric measurement.

As can be seen on this slide, the change in knemometry did not correlate at all to the growth velocity

on the y axis. You can see that the minority, of children showed a decrease regarding knemometry; whereas, the growth for the group during the 12 month were very similar to expected values for healthy children.

But this study illustrates what I think has been said a number of times this morning already, that there is great difficulties or impossible to extrapolate longer term growth from shorter term studies and similar findings have, indeed, been reported by other investigators.

Furthermore, the predictive value, as has been said this morning, for a final height by growth studies of one or even several years are quite limited and as reported by Carl Varing(?), whose work is in Sweden, a one year observation period had a predicted value with regard to final height of only 26 percent and even a four year observation time of more than 38 percent.

so, I think it is very important that we remember that extrapolation from short and intermediate data of growth observation to true long term or final height should be done with extreme care.

And with regard to potential effects of inhaled steroids on growth, the most important information clinically must, of course, be to get prospective final height data on children who had been treated with inhaled steroids during a substantial part of a childhood. Such

data is of understandable reason not easily or rapidly achieved but -- and have not been available until very recently.

At the ATS meeting in Chicago early this year, Soren Pedersen's group presented final height data on the first 31 children from their pediatric report of 216 children treated long term with Budesonide. I want to emphasize again that these are very recent data, which the FDA have not had a chance to review in any detail.

This cohort was established in **1986** by the consecutive enrollment of children at one center. The first 31 patients that were reported at ATS had been treated for at least seven and up to eleven years with inhaled Budesonide and their daily average dose was between 22o and 750 microgram via PMDIs or Turbuhaler until reaching final height and growth was measured by stadiometry.

This slide illustrates the relation between the predicted heights, based on the mean parental height and the observed height in these 31 children. This is clear from the graph there is no trend to an effect of Budesonide on the final height in these group of patients.

Thus , these patients achieved a predicted final height despite their asthma and despite that they were treated with inhaled Budesonide during a considerable part of their childhood. The final height was not correlated to

the average dose and it was not correlated to the duration of asthma or to the duration of Budesonide treatment.

Now , moving back to growth velocity studies, since the introduction of Budesonide in 1981, Astra, as well as independent scientists have studied growth velocity in children treated with inhaled Budesonide in different formulations in prospective trials. Some of these studies are available in the scientific literature are admittedly and understandably small and consequently some of these studies don't have the statistical power to detect very small differences but may still be of value to validate whether there was a substantial effect on growth or not.

I am not going into more detail of these studies but just want to conclude that none of these studies did report a significant effect on growth.

Moving over to new and unpublished on Budesonide inhalation suspension, inhalation suspension for nebulization of Budesonide in infants and young children is currently on review by FDA and the product is called Pulmicort Respulse. There have been three 12 week pivotal clinical studies carried out in the U.S. to compare efficacy and safety of these products with placebo in children with persistent asthma into **age** range from six month to eight years . The 12 week double blind studies were then followed by an open label safety extension where patients were

invited to take part and in which growth was evaluated.

To put this in perspective, I will just give you some data on the double blind part of the study. This slide show the baseline characteristics for the three studies. You can see that there were other population characteristics . There were more than 1,000 patients enrolled in the double blind program and about half of these patients agreed to enrollment in the open label follow-up studies.

The demographics were similar across the studies , and previous use of steroids was not permitted in one study, required in one study and optional in the third study. This slide shows the effect with regard to improvement in nighttime symptoms. Very similar results were achieved with regard to daytime symptoms and the need for rescue bronchodilators.

You can see that in all three studies we got compared with placebo prominent and significant effects compared with placebo. This was once a day dosing. This was the AD dosing and this study had both the AD and once a day dosing. The lowest dose here, 0.25 milligram once daily was not significantly different from placebo; whereas, the same dose in this milder group of patients showed statistical significance.

There were no clinically relevant differences in

the type, incidence or severity of adverse events compared to placebo and there were no evidence of HPA axis suppression measured as basal and stimulated plasma cortisol.

Afterwards we double blind the patients that wanted to continue were rerandomized to two week open label treatment in which group was assessed. This slide summarized the data from these studies with a change in the standard deviation score on the y axis, the red or Budesonide and the yellow or conventional asthma therapy.

It should be noted first of all on the numbers here that there was 1 to 2 randomization and the growth data, it was an even bigger difference because the withdrawal rate was significantly higher in two of these studies. In this study there was a small but statistically significant differences in growth rate of about 0.8 centimeter.

This study will be, I guess, discussed also in more detail in the presentations tomorrow. I do want to point out that in the two other studies there was no sign of growth defects at all. I think that the difference in withdrawals is also an important issue to consider and I think that patient withdrawals is a problem, which may occur in any long term asthma study as withdrawal rates are usually lower with a more effective treatment. And at the

same time, it introduces a difficulty in the interpretation of growth data as the level of asthma control may affect growth velocity as has been mentioned earlier this morning.

I also want to point at the fact that the control groups in these two studies did allow for use of steroids as well, which may have compromised the growth comparison. But the children in all these studies show the growth, which was as expected from national growth charts.

We also performed an analysis of all the three studies and with that we didn't see any significant effect at all.

Budesonide, as other inhaled or intranasal steroids has some degree of systemic absorption and a potential for systemic effect should never be neglected. With regard to the specific issue of growth effect, this is from a methodological point of view as we have thoroughly discussed this morning very complex, especially as uncontrolled asthma is likely to have an impact on growth.

It is also difficult to assess the clinical meaning of small changes in growth velocity as a predicted value with regard to final height is very low. We find the recent final height data, therefore, to be very important and very reassuring even if further data collections should be performed.

The accumulated experience of Budesonide used

according to the recommendation supports the conclusion that the overwhelming majority of asthmatic patients can be well controlled without adverse effects on growth.

But it is, indeed, important that potential effect of growth are defined and communicated to avoid inappropriate treatment. At the same time, these issues must not be overemphasized as that could definitely lead to undertreatment of asthma with unwarranted consequences on asthma control.

Our current labeling and package insert acknowledged the potential for effects on growth. Monitoring growth is recommended and dosing should be according to disease severity and individual need.

The current labeling is basically in line with the proposed class labeling from FDA.

So, to summarize, your studies, as we have discussed this morning, are complex and prediction of final height from shorter term studies is difficult. The overwhelming majority of patients can be well controlled without adverse effect on growth. And undertreatment of asthma is a major contributor to mortality and morbidity and inhaled steroids have been proven to be the most effective way of controlling the underlying inflammation in asthma.

As I stated in my introduction, we are in agreement with FDA that the risk of systemic effects should

be kept in mind when treating with inhaled steroids and that adequate information and precautions regarding this should be part of these products' labeling.

However, with the extensive clinical experience and large number of prospective clinical studies, now also including final height data, it is Astra's position that the risk for clinically meaningful effect on growth is very small and that it is by war outweighed by the outstanding level of asthma control offered by these class of compound.

We should never neglect the fact that poorly controlled asthma constitutes a significant safety issue in itself . Therefore, we believe that any labeling should reflect the positive benefit risk ratio of inhaled corticosteroids.

Thank you.

[Applause.]

DR. LI: Thank you very much for that presentation, Dr. Unman. We do have a few minutes for questions and answers and I will ask the committee members or guests for questions for Dr. Unman.

Yes, Dr. Gross.

DR. GROSS: A very brief question, Dr. Unman.

Did you measure compliance with the medication usage in any of those three studies that you just reported on?

DR. ULLMAN: The compliance was about 85 percent.

DR. GROSS: You mean, this is self-reported by patients or did you weight canisters or --

DR. ULLMAN: [Comment off microphone.]

DR. GROSS: Do you mean that the patients took 80 percent of the recommended dosages?

DR. ULLMAN: [Comment off microphone.]

DR. LI: Could I ask you, Dr. Ullman, are you able to estimate what the lowest effective dose of the Budesonide by inhalation might be patients with asthma of various severities?

DR. ULLMAN: I guess we are all aware of the difficulties in getting clear dose response relation with this class of compound. If we look at the data I showed on the inhalation suspension, I think we found in the medium, moderate group of these studies that a lowest group, 0.25 milligram of the suspension was not effective; whereas, that had an effect in the somewhat mild population.

So, I think that shows that we are in the range close to where we would lose effect if we came lower. I think with the huge inter-individual variation in dosing required, I think it is difficult to get -- and I think that mean response in this respect would be of a limited value for the individual treatment situation.

So, I think that we will continue -- have to

continue to rely upon individualized dose titration also in the future.

DR. LI: If I recall the slide and the data correctly, in the study that you reported in patients with mild asthma,the lowest dose that was studied was .25 milligrams once daily, which was shown to be effective compared to placebo but virtually identical to much higher doses. So, it is conceivable that lower doses of Budesonide by inhalation would be effective in those patients with mild asthma.

DR. ULLMAN: It cannot be excluded but we saw in our studies that the same dose was automatically -- so, I think we are at least not too far from a threshold here. Again, I think that what we have to do is to on an individualized basis titrate the dose down to the lowest possible to maintain the effect.

DR. LI: Let's see. Dr. Liu and then Dr. Crim.

DR. LIU: This is a short question. How was the final height predicted in the height study data that you showed?

DR. ULLMAN: [Comment off microphone.]

DR. PEDERSEN: It was the mid -- we also did as the Dutch recommend an addition, 2 centimeters for the mid-parental because of generational changes.

DR. LI: Dr. Crim.

DR. CRIM: On Slide No. 14, you presented your data as a change in standard deviation score in height. Could you explain for me what is standard deviation score?

DR. ULLMAN: I may leave that question to our statistician, who has made the calculations.

DR. MONTY: The way we did it was we took the patient's height, subtracted out the median height, divided by an estimate of the standard deviation. I know that is not the usual -- standardized score. We took the Z score at the beginning and then the Z score for their age and gender at the beginning and the Z score for their age and gender at the end of the study and when we did change in Z scores -- for example, a child who was 1 standard deviation below the median at the beginning of the study and who was 1 standard deviation below the median at the end of the study would have had no change in the Z score.

Does that answer your question?

MR. MADOO: Excuse me. Could the Astra statistician please identify herself by name?

DR. MONTY: I am Kathryn Monty.

DR. ULLMAN: As I mentioned, the difference in millimeters was 0.8 centimeter.

DR. LI: Thank you.

Dr. Cara.

DR. CARA: In your final height data, you present

essentially final height measured versus predicted. Were you able to get any intermediate points between the time when patients were first started on therapy and then, say, yearly predicted heights and evaluate how the predicted compared to the measured to see if there was, in fact, a downsloping, which tended to correct itself later or whether or not the measured versus predicted height was always along the line of identity?

DR. ULLMAN: I don't know if Dr. Pedersen will comment on that. It is your study.

DR. PEDERSEN: Yes, that is possible because this is an ongoing study and I am going to present some data from it also. We have height measurement every six months for ten years in this cohort. So we can do these measurements, but I don't have the data here today. We have decided not to analyze them until we have about 70 patients who have reached final height, not to get too low power.

DR. CARA: I would encourage you to do that primarily because we are interested in tracking growth and tracking actual heights since final adult height may be an ultimate representation of any potential attenuation and then any possible catch up that may be occurring.

What I am trying to say is that ultimate adult height might just be a washout and it would be interesting to see points along the curve, if you will.

The other question that I have is in your clinical trial that you presented, in the open label one year growth study, did you also evaluate the efficacy of Budesonide in terms of symptoms? I guess what I am getting at is that the one question that I would have --

DR. ULLMAN: In this stuff, both the conventional therapy and the Budesonide therapy was individually adjusted based on the symptoms. So, the task for the investigator was to adjust the therapy to control the asthma and the level of efficacy were relatively similar between the two treatments throughout the study.

DR. LI: Thank you very much, Dr. Unman.

Our next speaker is Dr. Shah, who is speaking for Glaxo Wellcome.

Agenda Item: Industry Presentation -- Glaxo Wellcome

DR. SHAH: Good afternoon.

What I would like to do today is give you an overview of some of the clinical information that we have on the two products that we market for the treatment of asthma and rhinitis in children. These products, as was reviewed earlier by Dr. Jenkins, are beclomethasone diproprionate or BDP and fluticasone propionate or FP.

The thing that I think is of note with these two drugs is the recommended dosages of fluticasone, both

intranasally, as well as inhaled, are 50 or a hundred micrograms twice daily in young children. These are the doses that have been found to be effective for a majority of children.

These doses are also lower than beclomethasone and I will refer to why those are important considerations when we review some of the data. As I said, without slides it makes it a little challenge. So, if you would bear with me, I think we are going to have to -- if we can't get a slide, we do have overheads that we can use.

DR. BARANIUK: Dr. Shah, your second slide will state "Intranasal corticosteroids with low systemic absorption. " I am sorry. You bring up the point of systemic absorption of intranasal steroids. Is there any information on what percentage of an administered dose is actually absorbed into the systemic circulation for the currently approved intranasal steroids?

DR. SHAH: What I can speak to is our two products, which are beclomethasone or Beconase and Flonase. We have studied the intranasal absorption of Flonase in numerous studies and the bottom line is that it is almost impossible for us to measure it at the recommended dosages that we use in children or adults. Part of that is because of the properties that I will talk about of these molecules are unique and different.

Let me just get started. I will speak to that question. I think the issue here is -- what I will try to cover today in my presentation is I think what you have all been discussing and hearing so far is that conducting and interpreting growth studies is a real difficult thing and we have to realize that there will be confounders when you do these kinds of studies.

And when you analyze the data, you have to consider these confounders, such as children who enter puberty during the trial or children who withdraw due to worsening asthma in the interpretation of these data. Additionally, I think we have to realize that these drugs are not all the same. The physiochemical and pharmacological properties are different and, thus, effects on growth may not be the same either.

Finally, the other comment is that intranasal steroids, such as the newer ones, which are not absorbed intranasally to a significant effect, are unlikely to have an effect in growth. And, finally, we have to, as everybody has been recommending, balance our discussions of safety in the context of the benefits, as well as we have to realize that this benefit to risk ratio is going to differ based on asthma severity.

so, in patients who were more severe, higher doses of inhaled corticosteroids or intranasal corticosteroids are

also maybe appropriate and outweigh the potential safety concerns .

Now , as I indicated, we do have two products, BDP and FP, and I think the most important point that I wanted to highlight was that in children the doses that we have found to be very effective are lower for FP because of these unique properties. FP is a newer corticosteroid and it was designed to have some unique properties, which make it a -- give it an improved therapeutic ratio in the management of asthma and rhinitis.

First of all, it is a very high glucocorticoid receptor binding affinity, which allows us to give very low doses for clinical effects. It has an inactive metabolize and the total systemic bioavailability is less than 1 percent through the oral route, less than 2 percent with Flonase intranasally and about 13.5 percent with Flovent Rotadisk when it is inhaled.

Now , in the development of FP in the U.S. , we actually conducted a rigorous growth trial to understand the effects or potential effects of growth with this product. And we studied about 300 children in these three treatment groups and for one year of treatment.

The other thing that we did in this study was we actually monitored their baseline growth for about six to eighteen months before they got randomized to treatment.

The other thing that I would like to point out is that this study was also used to support the safety of Flonase with regards to growth because its absorption into the systemic circulation is so much less.

We actually optimized the study for looking at growth by adjusting for -- or trying to minimize the impact of problems that we have encountered in the past in doing growth studies and interpreting them. One was that we tried to minimize the effect of puberty by doing two things; one, restricting the age group to try to ensure that we didn't have -- we were not enrolling children at an age where they would go into puberty. The other was to use Tanner staging and that was quite a challenge since most of our specialists were allergists, but they did the best they could and we did get, I think, useful data.

Children who had Tanner staging of less than 1 were -- 1 am sorry -- greater than 1 were excluded from the study and if they were high centile was also monitored to make sure that they were growing normally by making sure they were 5 to 95 centile for height and growth velocity because we monitored at baseline, was within 10 to 97 centile.

We excluded the medications known to affect growth, such as ritalin, and we tried to limit the prior systemic corticosteroid exposure in order to ensure that

didn't confound our results. We also, unlike other studies, used Harpenden stadiometers and performed these measurements at every four week intervals. These were very rigorously controlled over the course of the study, as you can see.

The other thing that was unique to this study was that we actually looked at Tanner staging for assessing sexual maturity, both at baseline, but also during the study. And patients who had Tanner staging greater than 1 during the study were allowed to continue. So, if they went into puberty, we did not withdraw them. However, we did -- the reason for this was primarily so we could look at those patients who did not enter puberty during the study in order to get an effect of treatment.

The statistical methods was that we used growth velocity as our primary measure to assess the effects of treatment. The caveat with this is that we looked at growth velocity by doing a two point analysis, which is that patients who had measurements of 28 or 52 weeks, their values from baseline or these values were subtracted -- the baseline values were subtracted to get the growth velocity at these two periods. So, we did not look at all the height measurements in the middle in assessing growth velocity and that is certainly -- I think we can touch on that, which makes it a challenge when you are trying to adjust for potential dropouts.

Finally, we had planned up front because we know puberty affects growth to do a subanalysis of those kids who did not go into puberty during the study. The power calculations of this study were adequate to be able to detect a 1 centimeter difference with 80 percent power.

This is the baseline asthma demographics. What I would like to just orient everyone is I will be showing you results in this format pretty much for most of the slides. Placebo will be in white; FP50 in yellow and the FP1OO in light blue. You can see there were adequate number of patients who entered the study and the overall demographic and asthma characteristics for these were pretty similar between the groups at baseline.

Now, as I indicated, while we did do everything we can to minimize the effect of potential confounders, we did have two, which I think will be a challenge for any prospective study that is being done to look at this issue. One is that we had an imbalance of the number of children entering puberty between the groups. And number two is we had an imbalance in the number of children withdrawing, due to worsening asthma between the groups.

Now, this is the slide that is showing the effect of the confounder of children entering puberty. The mean age between the groups was pretty similar, but as you can note, we had a lot less 11 year olds just by chance in the

hundred BID group. What that resulted in, you can see, is that the hundred group had about half as many patients going into puberty as the other two groups.

As we had all said, you" know, as has been discussed, when children are entering puberty, their growth is going to accelerate and, thus, these differences in between groups can confound the interpretation of the data. The other confounder was that we had more patients in the placebo group who withdrew due to worsening asthma.

Now, on average, if you look at the growth velocity of these children -- now, again, remember these withdrew, so you are going to have to do it using regression, as I will mention later on -- but if you look at the growth velocity of these children, what you find is that at baseline,. it was lower than the overall population. And for where you can measure it prospectively for those patients who have some values, it was slower than the overall population as well.

so, certainly, asthma itself, worsening asthma or uncontrolled asthma, had an effect on these results as well.

Now, here are the results of the overall data, which includes all patients. And it is a busy slide and let me orient everyone to these data.

This is the mean growth velocity for the placebo, the FP50 and the hundred group and at baseline the -- from

baseline to week 28 or the first six months roughly, week 28 to 52, the second six months of study and finally the whole one year period.

Now, what I would like to draw your attention to, again, is that at baseline and six months, there is no differences between groups in terms of their growth velocity. And what happened is in the second half of the study, these two groups -- these are the two groups that had the confounders. Remember, this group -- these two groups had more -- the two curves of the two groups had substantially -- had a higher number of children entering puberty and, remember, the placebo also had less number of children or more children withdrawing due to worsening asthma. So, their growth velocity data is not in here, the slower growing kids.

And the net effect of this was the difference between the hundred and the placebo was statistically significant in the second half of the six months, which then also contributed to the overall results out of one year to be statistically significant.

Now, what I would like to note is this difference here is about .66 centimeters between the placebo and FP100 group. The difference between these two groups, the 50 and the placebo was about .25 centimeters and at no time was that difference statistically significant compared to

placebo.

Now, let's see what -- in addition to doing that analysis, as defined in the protocol, the FDA requested that we actually look at the distribution of the growth velocity to try to get a sense of what is going on in individual patients. What I am showing you here is the two FP groups, the yellow is 50 and the blue is the hundred.

Then the pink here is the mean predicted height velocity that we would have expected the children in this study to have, based on using the Serona(?) growth charts. I think what you can see clearly is that the expected growth rate or the actual growth rate velocity in the FP groups coincides exactly where we would have expected it to be. Again, the curve around this is reasonably symmetric.

Now, this is the -- we have added the placebo group in this one and what you can see clearly is that the placebo group is shifted to the right of that what we had expected and the curve is not as symmetric as the other two. The part of this shifting or this skewing of these groups is a reflection of the confounders, meaning the placebo group doesn't have some of the slower growing kids, who withdrew for worsening asthma, as well as they have more kids on average compared to certainly the FP100 group who entered puberty.

These two confounders tended to shift this peak a

little bit to the right. Now, in order to adjust for the confounder of children entering puberty in the study, what we did was looked at the growth as we had planned in the prepubertal patients, meaning the children who did not enter puberty during the study.

As you can see, again, the same format as before, these two treatment groups, the second half of the study, you can start seeing that it does come down as you would expect because you have taken out the children who were entering puberty; whereas, this one doesn't change us as much as the other groups.

The net effect of this is that these differences are now becoming statistically insignificant. At the overall one year, these were also not significantly different and the differences between the 100 and the placebo group now is .43 centimeters.

Now, we struggle with how to try to adjust for the confounder of differential dropouts and what I have proposed to you and for you to consider is that this might be one way to at least try to address that issue. What this is showing you is the slope of the regression line for two patients who were enrolled in the study. Here is the patient who only made it to about 24 weeks and here is a patient who made it out to a year.

As you can see, the slope of the regression line

is really a change in height over change in time, which is the slope of growth velocity. Because it includes all the data points for the individual patient, even the ones who have one year of data, it probably represents a more robust measurement or assessment of growth velocity over the interval than to just look at the week 28 in baseline or the week 52 in baseline values.

So, we did this analysis to try to at least partially adjust for this confounder and these are the data. This is the prepubertal patients using the slope of the regression line. Again, what you can see is there were no significant differences between groups when you do this. The difference between the placebo and the FP100 group now is .38 centimeters. But what I would like to point out is because a lot of -- 12 out of the 20 placebo patients who withdrew for worsening asthma actually dropped out within the first six months of the treatment and, thus, we did not have their -- we could not calculate a reasonable regression line for those patients to include them in this measurement.

So, you can imagine that if we were able to include all the patients who withdrew for worsening asthma by this analysis, we probably would have gotten these numbers to be even closer together.

Now, I think a lot of discussion this morning has evolved around, certainly, BDP and the effects that have

been observed in several trials regarding its affect on growth. Dr. David Allen reviewed four of those studies and actually I believe tomorrow's FDA review will highlight that these were considered reasonably well-designed studies and four of them showed an effect.

It turns out they were all with BDP. I think the point that I would like to make is that these studies in general were all done at the high recommended dose of BDP for children and overall I think there certainly is a lot of evidence that it is difficult to dismiss in terms of these short term effects. But what I would like to do just briefly is review this one study with you in more detail, which is also going to be presented tomorrow by the FDA.

This is a study that was published in The New England Journal of Medicine by Dr. Simons from Canada and the objective was to look at methacholine responsiveness during one year of treatment with BDP placebo and Salmeterol. There were an adequate number of children in each group and the age was 6 to 14. They didn't really assess baseline growth or pubertal status during the study. However, they did measure height measurements at three month intervals using stadiometers at most of the sites.

Now, what I have shown you here are the results of the BDP data presented as mean change from baseline in height and on the right side is the same data presented for

the FP study. Now, we realize that this is not an appropriate way to make absolute claims about these two drugs in terms of their effects of growth.

We certainly support the FDA in that the only way we can make conclusive claims about differences is doing head-to-head comparative studies. But I think what this does tell you is some of the caveats that I would like to highlight in what I am going to say in terms of how these drugs do differ.

First of all, remember, this is all the patients' data. So, this is not adjusted for any confounders. What you can see, obviously, these two are different in terms of what we are seeing in the effect. The most important point that I would like to make is the BDP study in this one, as well as all of the ones that have been done to date that have shown an effect, the effect is fairly quickly seen.

Within the first six months, it is obvious that these two treatments are different and, indeed, in many of the studies the differences are pretty marked within the first month of therapy. What I would like to point out here is this point. If you look at the FP study, what YOU see is there was no difference. They were almost identical up to the first six months of therapy.

It was only in the second part of study where there was a slight separation between groups, which again

we have to be very careful that we don't paint the whole class with the same brush because there are going to be differences because the physiochemical and pharmacological properties of these drugs are different.

Finally, as I mentioned, Flonase, because it is not absorbed substantially systemically, it is unlikely to affect growth in children. I think this also needs to be an important consideration when we talk about class labeling. Because Flonase is also unique and there is one other steroid, momentasone, which are not absorbed substantially intranasally. So, their safety profile will obviously, be different than the older generation products.

Finally, I think, as everybody has been talking about, we need to be careful that we balance the safety risk discussions and consider the benefits of treatment, as well as the risks of undertreatment. I think it is clear that the safety risks are related to the dose, the drug, the route of administration and are related to systemic absorption, which all these things can affect. and they can be monitored, as many people have talked about.

We also talked about benefits, as Dr. Shapiro indicated, that these drugs are the most effective treatments for inflammation and that they have been shown to decrease morbidity in the management of these diseases. So, these diseases have serious health consequences when they

are undertreated.

The unfortunate thing is the use of inhalant intranasal steroids in the U.S. is underutilized and I think we can all realize that those also have substantial health consequences . I think while it is important for us to raise the awareness about the safety of this class of therapy, I think it is equally important that as health care providers, that we also raise the awareness of the benefits of this class of therapy so that we ultimately achieve the objective that we are really all here for, which is to improve the care and well-being of children with asthma and rhinitis in the U.S.

Thank you.

[Applause.]

DR. LI: Thank you very much, Dr. Shah.

We have really a full ten minutes for questions for Dr. Shah. We will start with Dr. Osborne and Dr. Kreisberg.

DR. OSBORNE: I have a question about one of the tables that is called “Mean Growth Velocity, ” in prepubertal patients. My question has to do with the sample size and power calculations. Once you are removing some patients from the study, which you did in this case because they had achieved puberty -- the sample sizes aren’t given but I estimate” them from a previous slide as being in the 80 to 90

range, two of the groups having about 80 patients, maybe less, and the initial sample size calculations' were set up so that a significant difference would have occurred with 80 percent power and an alpha of .05, only if there were at least 90 people per arm.

SO, my question is: Is one reason we are not seeing significant differences, could one interpretation be we simply don't have the power to see them based on the initial sample size calculations?

DR. SHAH: I think that is a very important question. Let me address that. First of all., let me also clarify then -- did you notice the difference that we observed in the second, exactly .66 centimeters. Based on our original power calculations, we should now be able to show that was statistically significant. What we found is that controls actually resulted in over power. SO, the rate was much smaller statistically than we had anticipated.

The factor that went against us also was adequate for us to be able to detect a difference. So, if there was a difference of approximately a centimeter, we would have been able to pick it up, based on the same size.

DR. KREISBERG: Dr. Shah, I wonder, do YOU have any information on the systemic effects of inhaled fluticasone? For instance, have you looked at white cells, lymphocytes or have you looked at basal cortisol levels or

stimulated cortisol levels to get at this issue of whether or not there is a systemic effect?

DR. SHAH: Yes, we have done those and both of those, but let me speak to the cortisol data because I think that is something that is relevant to our discussion. I don't quite know how to interpret the white cell data and I will defer that to somebody else from Glaxo Wellcome, if you are brave enough to come up and speak to that.

But in terms of clinical effects, the doses that were recommended in children, 50 to a hundred. twice daily, we have not been able to show effects on, substantial effects on cortisol. Indeed, we actually did look at urinary cortisol in this study. However, we did an overnight collection and it wasn't very well-monitored. So, the examples -- we had a lot of variability and the results were difficult to interpret.

There were no significant differences but still, I think, there were trends and it was hard to know whether that trend represented an effect or whether it was just a noise because of the collection of the samples. What I can say is we have subsequently done additional studies where we have controlled this much more rigorously in terms of the urine collection in children. And in those studies at these dosages we have not seen effects on urinary cortisol.

DR. LI: Any other questions for Dr. Shah? Yes,

Dr. Malozowski.

DR. MALOZOWSKI: In the control group there are two confounding factors. One is purity that clearly you can detect what about the other one that you mentioned. HOW do you know that patients that drop out were growing at slower rates than any other patient?

DR. SHAH: I think those are important questions and we, as I have said, have struggled with how do you control for the confounder of withdrawal due to worsening asthma because those will occur in any prospective study in looking at the effects in a disease.

The issue is that when we looked at the baseline work with those kids who withdrew, it was actually lower than the mean patients -- the growth velocity of baseline data in the overall population, which clearly indicated throughout that these kids whether it is their disease or whether it is something else were growing slower than the overall population.

The other thing is when you followed those few patients you have at maybe six months to eight months of data before they dropped out, those kids are growing at a slower rate than the overall population. So, those two pieces of information gives us some confidence that, indeed, that was a confounder that affected the interpretation of these data.

DR. MALOZOWSKI: Although I will be the first to accept that you cannot make cross studies comparison, in the other study, the placebo group grew better than the patient with beclomethasone and probably there also you had some little doubts how can you reconcile these two issues.

DR. SHAH: I think that is a very important point. Certainly, as I said, those studies or those comparisons were done to just give a relative comparison that these drugs pharmacologically are different and the issue would be that unlike fluticasone, which is metabolizes inactive product, BDP actually metabolized in the lung. So, it is very different in terms of its profile compared to the other corticosteroids.

so, I think what that difference in pharmacology also translates into these differences that we see when we compare them to this study, what I will say is that we are actively studying this further. We do have recent data that we will be sharing in the near future, which I think will confirm what we have been saying, that these corticosteroids are not the same.

DR. MALOZOWSKI: By no means I am comparing the corticosteroids. I am only comparing the control groups. It is true that in the control group in the fluticasone, the patients were dropping and those that were dropping were going slower. How do you reconcile this with the fact that

the patients in the placebo group in the other study were growing better than the ones treated with active drug?

DR. SHAH: I think what I would say there is, I mean, that study -- the data that is presented there is actually as regression analysis. So, it includes any data that we have up to the point where they were withdrawn.

DR. MALOZOWSKI: Okay. That is fine.

DR. SHAH: So, you are including a lot of the data in equal amounts in the various groups.

DR. LI: Courtney.

DR. CRIM: Just one question in terms of the study design regarding the patients who dropped out because of the worsening of asthma. My question is what constituted dropping out for worsening of asthma? Was it a person needed a dose of systemic steroids or if they required a dose of systemic steroids for a short period of time, were they allowed to stay in the study. What compelled them to be dropped from the study?

DR. SHAH: The study design was such that we allowed children two episodes of bursts of systemic corticosteroids before we would withdraw. It could only be less than seven days or if they needed more at any time, then they were out. So, the overall exposure for corticosteroids in the study was pretty small.

However, as you would expect, there was a greater

amount in the placebo group. But the think that I would recall -- would like to draw your attention to is that when the placebo patients who had two bursts dropped out, their growth velocity analysis is not included in the data that we are looking at in all patient analysis.

That could be the confounder. We don't know if it was the asthma itself in those children who withdrew and were growing slowly or it was the actual steroid bursts or a combination of the two that was contributing to their growth being slower than the other kids.

DR. CRIM: Were steroid bursts allowed during the baseline period?

DR. SHAH: No.

DR. CRIM: What was the maximum dose of the steroids that they could receive, as far as the two doses of bursts?

DR. SHAH: The corticosteroids?

DR. CRIM: Yes, the oral --

DR. SHAH: It wasn't controlled. It was up to the investigator's discretion.

DR. CRIM: Do yOU have any data in terms of what was the max that was used? I am just trying to get a feel in terms of how much steroids --

DR. SHAH: We tried to look at that. but it was very difficult because some people, you know, were treating

-- I mean, everybody has their own way of bursting. So, I can't recall exactly what the highest dose, but I think it was on the order of about a milligram per kilogram for these kids .

DR. LI: Last question for Dr. Shah from Dr. Gross.

DR. GROSS: The first question is very short. I assume that you got some measurement of efficacy from the FP study showing that even in the doses that you used here, you did have an affect, a beneficial effect on asthma. In other words the patients did respond as you would expect in terms of asthma symptoms.

DR. SHAH: Correct. This study, as well as many other studies, has shown that the 50 microgram twice daily dose of FP is highly effective in controlling the majority of children who need corticosteroids for asthma.

DR. GROSS: Right .

My other question is, you know, I am adult pulmonologist, not a pediatric pulmonologist. It may be that I am mistaken here, but these look like rather small doses. I understand that FP is more potent than other inhaled corticosteroids, but in an adult a hundred micrograms BID would be considered a fairly small dose. So, the question comes up if you use doses that are maybe at the upper end of the typical dosage range, might you see effects

that are not so pat here?

DR. SHAH: Are we talking about children or adults?

DR. GROSS: Well, obviously, it is growth. So, we are talking about children.

DR. SHAH: I think what I would say is that we studied these at the level of 50 and a hundred twice daily pretty extensively and feel very comfortable about the benefit/risk ratio of those doses. Certainly, higher doses are available and I am sure are being used occasionally in managing more severe asthma. But I think in those situations, we would urge that the appropriate benefit/risk assessment is made before those products are using beyond the recommended doses. Certainly, we would not, you know, openly advocate their use beyond what they are recommended.

DR. GROSS: Is there an upper limit to the dose recommendation for FP in children?

DR. SHAH: It is a hundred twice a day.

DR. GROSS: Oh, I see. Okay.

DR. LI: All right. Thank you very much for your presentation and your answers to questions, Dr. Shah.

Our third speaker for this afternoon is Ms. Plon from Rhone-Poulenc Rorer.

Ms. Plon.

Agenda Item: **Industry Presentation -- Rhone-**

MS. PLON: Thank you for bearing with us.

Good afternoon. I am Judy Plon. I am the director of regulatory affairs for respiratory allergy products at Rhone-Poulenc Rorer. On behalf of Rhone-Poulenc Rorer, I would like to thank the RDA and the advisory committees for the opportunity to present the Azmacort growth study and to participate in today's scientific discussion addressing pediatric growth on the orally inhaled and intranasal corticosteroid products.

Rhone-Poulenc Rorer supports FDA's initiative regarding the need to address class labeling across the orally inhaled and intranasal corticosteroid products. We look forward to the recommendations that will be coming from the committee with respect to this.

Currently, Rhone-Poulenc Rorer's products, Azmacort, which is used in the treatment of asthma, and Nasacore products, used in the treatment of allergic rhinitis, do contain a general precautionary statement regarding growth in the pediatric population.

I would like to provide you with a brief historical overview of the Azmacort growth study. The Azmacort growth study was originally a Phase 4 commitment made to FDA by Rhone-Poulenc Rorer several years following the approval of the Azmacort NDA. The protocol was

developed in close collaboration with FDA's Pilot Drug Division. This was the division that was responsible for the oral intranasal and orally inhaled corticosteroids at that time.

When the protocol was finalized, it was a one year, open label treatment and it was considered state of the art in the early 1990s. Today I would like to introduce Dr. David Skoner, associate professor of pediatrics and otolaryngology, Children's Hospital of Pittsburgh, who will present the Azmacort growth studies results.

DR. SKONER: Thank you very much.

Having treated numerous children over the last 15 years with these products and having participated in numerous growth trials over the years, I am really pleased to be able to present these data to this distinguished audience today.

The objective of this study was to compare growth over one year in groups of prepubertal children in three different populations: number one, a normal population; number two, moderately severe asthma patients maintained on one of two regimens, either nonsteroidal therapy or Azmacort therapy. Then a third group of severe asthma patients maintained on one of two regimens, either Azmacort plus prednisone, which I will call a combination group, or prednisone alone.

The differentiation between moderately severe and severe asthma patients was based on the 1991 NHLBI " guidelines, as well as investigator judgment. The design was open label, multicenter, randomized and stratified by severity.

The analysis included a primary population that we called "All-Treated." Those were patients that were in the study for at least ten months or 300 days. The sample size plan was 100 per group. That provided at least 90 percent power to detect a 0.68 centimeter growth difference with a standard deviation of 25 percent.

Inclusion criteria for entry into this trial were ages 6 to 10 years in girls or 6 to 11 years in boys. They were all at Tanner Stage 1 at enrollment. For the normal subjects and moderately severe asthma patients, they had to be between the 10th and the 90th percentile for both height and weight.

For the severe asthmatics, they needed to be between the 10th to the 90th percentile for height and at or above the 10th percentile for weight.

Patients were excluded for any reason for aberrant growth, major non-asthma organ system disease, current acute illness or severe illness in the past 30 days, non-asthma conditions potentially requiring long term oral, topical, systemic or nasal steroid therapy.

However, hydrocortisone topical cream was permitted in this trial.

Study procedures, all randomized patients were seen every four weeks for 52 weeks. The normal subjects were assessed every 12 weeks.

At the screening visit, patients had a history, physical exam, including a slit lamp exam and puberty exam. At Visit 1, which was within 14 days of the screening, they had a baseline height, weight, bone age and pulmonary function test. PFTs were not performed in normal subjects.

At this visit, the asthmatic patients were randomized for therapy. At Visits 1 through 12, a history and physical exam were conducted and a review of the diary. Medication adjustments were permitted based on these parameters. At Visits 4, 7 and 10, height, weight and pulmonary function tests were repeated. At Visit 13, in addition to the above, bone age and slit lamp examinations were repeated.

There was no follow-up puberty assessment incorporated in this trial.

The treatment arms were as follows: Normal subjects had no treatment during this trial. Moderately severe asthma patients were randomized either to Azmacort at a recommended starting dose of at least 400 micrograms per day or nonsteroidal asthma treatment. This was typically

either theophylline or chromalin.

Four bursts of systemic steroids for up to ten. days each were allowed in the study. After that, the patients were discontinued.

For severe asthma, they were randomized to either alternate day prednisone alone or Azmacort plus alternate day prednisone. The recommended starting prednisone dose was based upon investigator judgment with titration to effect allowed. There was no restriction in this group on systemic steroids for flares.

The Azmacort dose in both groups was allowed to be titrated to minimize adverse effects and mai:ntain effective symptom control. Compliance in this trial was assessed by diary cards.

There was a primary growth assessment here and a secondary assessment. In the primary analysis, height was measured by stadiometry very, very carefully. The growth difference in centimeters was calculated at the final height minus the baseline height. We also analyzed this as the percent predicted growth defined as the percent actual growth, divided by the predicted growth.

The final height minus the baseline height and the percent predicted growth was the percent actual growth divided by the predicted growth, the final study height here.

In the secondary consideration, bone age was obtained by plain radiographs. A blinded assessment by an independent radiologist using Greulich & Pyle was done. Bone age change in years was calculated as the final bone age minus the baseline bone age and we also calculated the percent bone age change defined as percent bone age change divided by chronological age change.

These are the patient demographics for the normal population, the moderate asthmatics and then the severe asthmatics on the right. First of all, regarding enrollment, you can see the normals in the two moderate asthmatic groups fulfilled their enrollment criteria. However, the severe groups fell short by more than 50 percent.

The percent completed was low in the prednisone group and it was also low in the nonsteroidal group. About seven patients fell out of the nonsteroidal group compared to the Azmacort, due to either asthma exacerbations or exceeding the predefined limit of steroid use.

By the way, these yellow figures don't represent statistically significant differences. They simply point me in the right direction.

Overall, in terms of mean height, mean bone age and mean chronological age, our groups were fairly well balanced. There are a few exceptions. The nonsteroidal

group here you can see was taller at baseline and a little bit older at baseline.

Overall, we had pretty good concordance between bone age and mean chronological age on study entry. The one exception was the prednisone group at baseline. You can see the mean bone age was lower than chronological age.

In terms of the age range, our limits were up to 11, but you can see some patients enrolled in this trial near their 12th birthday at enrollment. One difference on this slide that is significantly different is the gender mismatching in the normal population. You can see it is 50/50 distribution versus the typical asthma distribution in children in these age groups of three to one male to female distribution.

The FEV1 is shown on top here in terms of leaders and then percent predicted. You can see the percent predicted in the moderate group was about 88 percent, in the severe group about 94 percent. It is important to note that these were taken while patients were on their baseline medications prior to study entry and that may be why they are so high.

Nonetheless, they were on a lot of medications prior to entry in this trial overall. This is prior steroid use in terms of percent. This would be none. This would be inhaled steroids only. This would be oral steroids either

on a burst basis or alternate day basis and then this category is for both.

In terms of no prior usage, you can see about 25 to 30 percent of the patients in the moderate asthma group fit that criteria versus none in the severe population. As far as the moderate population, they were pretty well balanced as far as prior use in these two groups.

However, you can see that about 70 to 75 percent or so of the patients in the severe group were on a fair amount of steroids prior to entering this trial. These are treatment regimens by days treated in daily doses. You can see that overall the duration of therapy here, days treated, was over 300 for all of the treatment groups up here.

In terms of daily dosage, the mean Azmacort dose in the Azmacort group was about 600 micrograms per day with a range up to about 2,000 micrograms per day. In the combination group over here, you can see a higher mean Azmacort dose at about 757 micrograms per day with a higher range as well up to about 3,200 micrograms per day.

The range for the prednisone dose i:n this group was -- the mean value was about 8.9 milligrams every other day. You can see with the range of about 1 up to 75 milligrams every other day. In the prednisone alone group, you can see it was slightly higher average value at 12.2 milligrams every other day, with a range from 1 up to 3.58.

Now , that is a little bit striking, but that does was a prednisone equivalent dose used by one patient for one day in the study.

Here is a summary of the growth parameters. On the left, we will have a mean growth difference and on the right we will have a mean percent growth difference. In terms of mean growth difference in centimeters, you can see the normal population had a mean growth difference of 5.9 centimeters, 6.1 in the nonsteroidal group and 5.3 in the Azmacort group.

The difference between nonsteroidal and Azmacort was significant with a P value of less than .001. The Azmacort group was also significantly different from the normal population, but the nonsteroidal group was not.

The mean percent growth difference, you can see, was 106 percent in the nonsteroidal group, indicating they grew a little faster than expected and was about 93 percent in the Azmacort group. In the combination group, you can see about 5.5 centimeters mean growth difference versus 5.6 in the prednisone group.

There were no differences between these groups here and there were no differences between either of those and the normal population. The percent was very similar.

This is a growth velocity distribution in normals and the moderately severe asthmatics, who were maintained on

nonsteroidals or the Azmacort over here. This is growth difference on the vertical axis and we plotted the 50th percentile line, the third percentile and the 97 percentile, based on the normal population in this particular study.

We have males on the left and females on the right . This gives you an overall picture of the range for the normal population here, how you can see the nonsteroid population here as well. If we look at the Azmacort population, you can appreciate the effect we pointed out. You can see a small decrease in growth in this group. But you can also appreciate a lot of outliers. This was a widely spread out group.

Some of the fastest growers in this study were in the Azmacort group and some of the slowest growers in the study were in the Azmacort group. I think for females you can appreciate similar trends and spreads of the data. The exception, there is no outliers up here for the females in the Azmacort group and, if anything, there may be a little bit bigger effect here with females than with. the males.

We decided to regress growth over the mean daily Azmacort dose in micrograms. Even though this study wasn't designed to detect a dose response effect, the dose titration allowed us to look for that.

We have Azmacort patients shown by the pluses and the normal population shown by the squares, which you see

over here and the regression line is right here with 95 percent confidence intervals.

If we focus in on this range right here between about 300 up to about 800 micrograms a day, you can see some of the fastest growers were in that dose range and you can also see many of the slow growers were treated in that range as well.

We don't see a disproportionate number of patients up in this area in the higher dose ranges with low growth. We were able to calculate a P value for the significance of the slope, which you see up here and it was 0.21. The dose accounted for about 2 percent of the variance in growth in this study.

Here is the bone age parameters laid out in a similar fashion with mean over here being changed and percent change over here. The mean change in bone age years for the normal population was 0.9 years; 1.1 for nonsteroidals and 0.9 for the Azmacort.

This dip between group difference here was significant, P less than .001. In this case something different was seen than with growth though. The Azmacort population wasn't significantly different from normals; whereas, the nonsteroidals were. You can see their bones aged at about 109 percent of predicted levels versus about 88 percent for Azmacort.

In terms of the combination group down here, you can see it was .7 years versus 1 in the prednisone group. This between group difference was significant with a P value of .03. The combination group was also significantly different from the normal population.

We thought that since this study captured bone age change, we thought it was very important to put the decrease in growth into perspective in term of the bone aging. We had that opportunity here. So, we looked at a ratio of the percent predicted growth over the percent bone age change.

This is a log of that ratio on the vertical axis for the five different groups which you see here. We plotted the mean value of the normal population plus or minus two standard deviations. And, of course, there are about three ranges on this slide, a big range up here, where you might expect rapid growth, but delaying of bone **age.**

Down in this region, this would be where growth wouldn't proceed but bones would continue aging and this may not allow for catch up growth down here and, hopefully, somewhere around this zero line here, we have changes in growth and bone age that are the same. That could be a hundred percent over a hundred percent or it could be 90 percent over 90 percent, like we observed in this Azmacort study in the Azmacort group.

But, nonetheless, you can see the normal

population is pretty well distributed between, these lines, as is the nonsteroidal group and most interestingly the Azmacort group. The prednisone group and the combination group were also distributed within the two standard deviations.

Pulmonary function tests at endpoint, this is the FEV1 median percent change from baseline. You can see it was about 14 percent for the two moderate asthma groups; 8 and 11 percent for the two severe groups. There were no significant P values here.

This study was not designed as an efficacy trial. Nonetheless, patients treated with Azmacort had significant improvements in asthma control as evidenced by a reduction in steroid-requiring flares, school days missed, nocturnal episodes and number of play interruptions.

In summary, for children with moderately severe asthma, Azmacort therapy showed a small but statistically significant reduction in growth velocity versus the nonsteroidal therapy group, with a difference here of 0.79 centimeters, as well as the normal population with a difference of 0.59 centimeters.

For children with severe asthma, both combination and prednisone therapies, did not show a statistically significant difference compared to the normal group. The growth reduction paralleled that of bone age and was

observed in the context of improved asthma control. parallel reduction of both growth and bone aging may allow for catch up growth.

Inter-individual sensitivity in this study for the inhaled steroids appeared to be high. We thought it was important to compare the strengths and weaknesses of this trial compared to some of the more recent ones. In some cases, a factor that might be a strength might. also be a weakness, as you will see.

This study had two control groups, the normal population and the nonsteroidals. In terms of strengths, we studied a more severe population here than most of the other studies and a lot of dose titration, which really made this very much a real world setting type of study. It was well powered and very highly powered to find its effect.

The duration was reasonable. The stadiometry technique in this study was very good and it added bone age determination, which many earlier studies didn't have.

Some of the weaknesses were the baseline imbalances that I have pointed out, especially with regard to the normal population and gender. We didn't collect baseline growth rates in this study, although many other studies didn't as well. There was a variable steroid exposure here with regard to both inhaled dose of Azmacort as well as the oral steroids and there was no placebo or

blinding in this study and, importantly, no fellow-up pubertal assessment. There was also a higher dropout rate in the nonsteroidal group, which may have confounded interpretation.

In conclusion, the finding of a small but significant growth retardation was similar to that observed with other inhaled corticosteroids. The clinical relevance of these findings is unclear. Certain design elements in , this trial were not optimal and clearly further studies are warranted.

In terms of class labeling, existing data for oral inhaled corticosteroids are sufficiently compelling to support class labeling for all inhaled corticosteroids with regard to the potential impact on growth in children. However, this small risk should be balanced against the well-documented benefits of this class on morbidity and mortality.

Intranasal corticosteroids on the bottom here, in view of the limited database on the potential effects of intranasal corticosteroids on growth, it is recommended that additional data be collected before extending class labeling to these particular products.

Thank you very much for your attention.

[Applause.]

DR. LI: Thank you very much, Dr. Skoner for that

careful presentation.

We have about five minutes for questions for Dr. Skoner and we will start with DR. Osborne.

DR. OSBORNE: Apparently, there were some individuals who did have a decrease in growth velocity. Was it appropriate to do any post hoc analyses to determine if the susceptible individual could be detected or stood out in any way?

DR. SKONER: . That is a very good question. We looked at a number of different parameters including steroid use before coming in the study, oral steroid use. Oral steroid use while on the study, as well as age and a number of other factors, and really weren't able to tease much of anything out.

Three of the patients out of about 1.1 or so that dropped out actually -- and had low growth actually had a fair amount of steroid exposure prior to coming into the study . One patient had about 31 day bursts of prednisone just before coming into the study and a couple of others had about ten day bursts, but that really only stuck out in about 3 out of maybe 11 patients. So, we really couldn't tease anything out that would clue us into which those patients would be.

DR. LIU: I have got two quick questions. One is prednisone comes out looking pretty good here in this study

and I would like you to sort of comment about that.

Then the other question really has to do with whether you do have data about systemic exposure with intranasal use of Azmacort. I mean, you have done studies or there may be limited data but what kind of systemic exposure vis-a-vis inhaled corticosteroids to the lung. Do you have nasal applications?

DR. SKONER: I will answer the first part of that question. I think the prednisone and the combination groups are difficult to interpret their data. There is a small n compared to the others, first of all. If you look at whether, you know, oral corticosteroid use was spared when you added Azmacort, I would question whether it was because the average dose in the prednisone alone group was about 12 and in the Azmacort plus prednisone group it was about 9, with the added Azmacort on board, about 750 micrograms per day.

So, I question whether that actually went on. If you look at the pulmonary function test in the prednisone group and the combo group at baseline, you can see they were a little bit higher, about 94 percent versus about 88 percent predicted in the moderate asthma groups. So, I think taking any kind of information away from those groups or comparing that severe group to the moderate group in this study, I think, is very difficult for a number of reasons.

The second part of that question I am going to let someone else address.

DR. LI: You have about a minute, if you don't mind.

DR. ROSEN: My name is Jerry Rosen. I am with Drug Metabolism Pharmacokinetics at RPR.

We don't have data from the study that was just described in terms of systemic exposure in that study in pediatric patients, but we can provide you with some relative comparison here. What you see is systemic exposure for the oral inhaled product at the average dose of 600 micrograms that **was** in this particular study t-hat was just described.

You can see the C max and AUC values for those. They are here. Then we also have compared that for the recommended doses of the intranasal TAA, the AQ formulation, the aqueous formulation and **also** the CFC intranasal. These are the two recommended dosages in pediatrics and you can see, again, the C max and AUC values.

I guess the comment to make here is that systemic exposure with the intranasal products is lower than that would be oral inhaled.

DR. LIU: But the dose is different in these studies. I mean, if you use comparable doses, do you have any information about that?

DR. ROSEN: Well, the doses are different but these are -- again, this is the average dose that was used in the growth study that was just described. So, this is systemic exposure from that study at that dose and then these are the recommended doses for the intranasal products and this is the data we have at those doses.

DR. LI: Okay. Thank you .

We have time -- maybe a quick question from Dr. Gross and a quick response before we move on.

DR. GROSS: Well, actually my question was the same as Dr. Liu's.

DR. LI: Thank you very much, Ms. Plon and Dr. Skoner.

Our next speaker is Dr. Affrime from Schering.

Agenda Item: Industry Presentation -- **Schering**

DR. AFFRIME: Good afternoon, everybody.

I, too , would like to thank the two advisory committees and Dr. Jenkins for inviting us here today to share this information on beclomethasone nasal. spray with you . .

I would like to start out by just reviewing, as Dr. Jenkins mentioned this morning, that beclomethasone dipropionate nasal spray is used in adults and children for the indications of nasal and non-nasal allergic rhinitis and that the labeled doses are 168 to 336 micrograms per day.

We evaluated beclomethasone nasal spray for systemic exposure initially in adults, looking at bioavailability based on pharmacokinetics and HPA axis suppression and then indirectly as a Phase 4 commitment, based on 12 month growth study, in conjunction with Glaxo Wellcome and with a protocol that was developed in accord with the FDA.

Imbedded in that study, we also looked at HPA axis suppression. I would like to conclude later on with just some remarks.

Our pharmacokinetic study was carried out in adults, 24 healthy subjects participated in this study. They were treated for seven consecutive days with an 84 microgram BID product or 168 microgram product.. So, they received either 168 micrograms per day or 336 micrograms per day. For this study we used a very sensitive and specific assay. The limit of detection for BDP and 17 BMP was that 50 picograms per ml, that for 21 BMP and for beclomethasone was at a hundred picograms per ml.

Just to share the results, it is very simple, of the 768 blood samples that were assayed only seven samples were positive for BDP and we had one sample positive for 17 BMP . We concluded from these data that the drug was essentially not bioavailable in these patients.

Our HPA access study was carried out in adults.

It was a randomized, investigator-blind, placebo and positive-controlled, parallel group study. Sixty-four patients with allergic rhinitis participated in this study. There were 16 individuals per treatment group.

The treatment groups consisted of a placebo spray, administered twice daily, a BDP nasal spray administered at 168 micrograms BID for a total daily dose or the top label dose, 336 micrograms. And the third treatment group was the 336 micrograms given daily for 36 days. A prednisone, 10 milligram every day for 36 days served as a positive control. So, we had a placebo and a positive control.

The results were based on a cosyntropin 250 microgram infusion, a six hour infusion at baseline after 36 days of treatment. I present here the plasma cortisols over the six hour period in the baseline. As you can see there is no difference between any of the treatment groups.

This is the day 36 results. The one group that separates from the pack up here is the prednisone, 10 milligrams a day. The other treatments do not. separate from placebo and there is no indication of systemic exposure. Based on these two studies, we had no reason to think that there would be any exposure following the nasal spray administration to children.

However, we did have this Phase 4 commitment ongoing and I will present now the results of this study.

This was an evaluation of the effects of beclomethasone nasal spray on long term growth in children, a one year study . This was a very demanding study and it is due to the commitment by these investigators and Dr. Skoner can be counted amongst them, who diligently carried out this protocol and I thank them.

The objective of this study was to determine whether long term administration of BDP nasai spray affects growth, as well as its effects on the HPA axis in children. This was a randomized, multicenter, double blind, placebo-controlled study. We felt that placebo was the most appropriate control for this study.

We chose patients aged from six to nine and a half years old for boys and six to nine years old for girls and we felt that this was the most appropriate group because they were all prepubescent and they all had Tanner Grade 1 scores.

The results were based on stadiometric determined heights. They had to be within the 5th to the 95th percentile.

Also, in the inclusion criteria, we determined bone age based on x-ray of the left hand. That had to be within two years of the chronologic age. We felt that bone age, as well as a history from six months prior to the study to two years of normal growth was adequate to demonstrate

that the individuals who have participated had been growing normally up to the time of study initiation.

The individuals had to have a normal 8:00 a.m. plasma cortisol, as well as a normal cosyntropin response. They also had to have symptomatic perennial allergic rhinitis at baseline. This was not an efficacy study. It was not powered to determine efficacy, but we needed to have them -- we wanted to have them with moderate allergic rhinitis just to ethically participate in a year study.

Patients fulfilling the inclusion criteria were randomized to treatment with BDP 168 micrograms per day -- twice a day -- or the placebo group. These patients who were randomized were stratified at baseline with respect to gender and history of previous steroid use.

Following this baseline visit, they returned for follow-up evaluations at week 1 and then at months 1 and 2 and then every other month for the year. The stadiometric heights were determined at months 1 and 2, and then every other month for the year's duration of the study.

Cosyntropin stimulation tests were done, as I said, at baseline and then at six and twelve months.

Reviewing the demographic data with you, you can see that we did have baseline differences in age and height. The treatment group were slightly older and taller than the placebo group. Consistent with that was bone age, which was

marginally different in the BDP group, there was no difference in weight between groups.

And as I mentioned, we stratified for gender and previous steroid use and, obviously, there were no differences in that group. Racial breakdowns were similar also between groups.

Just to review the statistical methodology, growth rate was estimated for each subject as the slope of the linear regression of the height on time, which is the growth velocity that we have been talking about all morning. The secondary endpoint is the change in height by time, which was merely the change from baseline at each time point.

Analysis of the growth rate and by time actual heights from baseline height were accomplished by a two-way analysis of variance and we extracted for sources of variation for center and treatment.

As I mentioned, we did have that baseline difference, so we actually also carried out analysis of covariance looking at height as a covariate. This analysis did not demonstrate any change in the outcome.

Just looking at the intent to treat population, 51 subjects in the BDP group and 49 in the placebo, there was a statistically significant difference in growth. velocity between the two groups.

I mentioned that we also did a chart evaluation of

growth prior to the study, that is, the six month to two year evaluation and I just put this in to demonstrate that growth velocity prior to study initiation were similar between the two groups, based on this retrospective analysis. Then if you take the difference into consideration, there still is statistically different growth rate between the two groups.

Just to present the change from baseline relative to the time of study, you can see that the treatment group is different from the placebo group beginning at month 1 and then from month 6 through the end of the study. We get a stabilization of about 1 centimeter difference between the two groups by about month 10.

This may support the fact that a one year study may be necessary to carry out such an evaluation.

The cosyntropin stimulation test results, as Dr. Jenkins mentioned this morning, gave us no indication that there was any change or any systemic exposure based on these data between the two groups. Everybody had a normal response to the cosyntropin administration.

In summary, in adults, as I presented, BDP nasal spray was not bioavailable at doses up to 336 micrograms per day based on pharmacokinetics and HPA axis assessment. In children, the nasal spray caused a small but significant reduction in growth rate compared to placebo. There was no

effect of HPA axis as measured by the cosyntropin stimulation.

We feel that assessment of systemic effects in adults does not extrapolate to children therefore.

To conclude that class labeling regarding the potential of growth inhibition in children is appropriate for nasal and inhaled steroids; however, we feel that a product may be exempted from such class labeling if there is a negative 12 month growth study and a weight of evidence demonstration of no systemic exposure based on the following measures : knemometry study, HPA axis evaluation, potentially even a cosyntropin stimulation test. There is some information now that -- and as mentioned this morning -- that a low dose stimulation test may be more sensitive, as well as pharmacokinetic evaluation.

Thank you for your interest.

[Applause.]

DR. LI: We have a question already. Please, go ahead, Dr. Hirsch.

DR. HIRSCH: Just a simple one. Do you think this is not bioavailable in children also, I mean, as in the adults? Has the growth -- you understand what I mean. If there is no bioavailability in adults --

DR. AFFRIME: No, I think there is systemic exposure at these doses in children.

DR. HIRSCH: How do you know?

DR. AFFRIME: Because the growth --

DR. HIRSCH: I see. Well, unless there is something from the -- some new great thing we are learning about a connection between the olfactory nerve and the hypothalamus or whatever.

DR. AFFRIME: We haven't studied exposures in children, but these data indirectly would support that.

DR. BONE : Just to pursue Dr. Hirsch's question -- this is Dr. Bone speaking -- 1 think it might be more precise to say that systemic bioavailability could not be measured since it is stated it was not systemically bioavailable.

I mean, presumably -- I mean, the limitation here was the sensitivity of your assay presumably, not that there was not a single molecule absorbed.

DR. AFFRIME: The HPA axis suppression study at the highest labeled dose and the clear separation from the axis control is -- was strong evidence to us that -- as another indicator that there was very -- you have to say limited bioavailability if none.

DR. HIRSCH: But it may be different in children, where you didn't measure it, Isn't that true?

DR. AFFRIME: Yes.

DR. BONE: And the lack of the biological -- lack

of a clear cut effect on the HPA axis and the test that you employed is a different issue really than whether the drug was absorbed.

DR. LI: We have questions from Dr. Szefler, then Dr. Baraniuk, Dr. Cara and then Dr. New.

Go ahead, Dr. Szefler.

DR. SZEFLER: Two questions.

You had mentioned in your list at the end, cosyntropin tests. I know the six hour cosyntropin infusion test has been used and maybe the endocrinologists can comment on that in terms of where does it fit in terms of the reliability. I have had some experience with the low dose and I think that presents challenges in terms of methodology and the six hour cosyntropin was thought to get over the aspect of the high dose, 250 micrograms over-flooding the system. Does the six hour have any more sensitivity in separating out dosages?

DR. LI: Anyone care to address that?

Yes, Dr. New, please.

DR. NEW: I can't speak to the low dose, but I can tell you that we have shown that using the standard .25 dose, the six hour and the 60 minute tests are indistinguishable and their results in terms of serum steroid concentrations.

DR. AFFRIME: I think the literature supports that

conclusion as well. We did a six hour infusion testing in those adults, but we also have a 60 minute, the same test.

DR. SZEFLER: The other thing is I thought maybe you might present some data on mometasone. Do you have any data on mometasone in children in terms of growth studies?

DR. GLOVER: I am Dick Glover(?) from Schering.

At this time, mometasone is indicated only for patients 12 years of age and older. We are in the process of filing a pediatric NDA soon. As part of that, we have conducted a 12 month growth study, as well as a knemometry study, but, again, those data have not been submitted to the Agency.

I can tell you that at this point those two studies are negative, but, again, I don't want to give you details of those results until the Agency has seen them.

DR. LI: Next question from Dr. Baraniuk.

DR. BARANIUK: The absorption studies, those were in normal subjects?

DR. AFFRIME: The pharmacokinetic studies was in health volunteers. The cosyntropin stimulation test was in patients with --

DR. BARANIUK: The healthy volunteers are not the usually prescribed group receiving this drug. What is the absorption like in people with active allergic rhinitis?

DR. AFFRIME: We didn't do the pharmacokinetics on

those individuals. I have no data on that.

DR. BARANIUK: And could it be different?

DR. AFFRIME: Potentially. Since we haven't studied, I can't really answer.

DR. BARANIUK: It might be more useful.

DR. LI: Thank you.

Next question, Dr. Cara, question or comment.

DR. CARA: I am intrigued by the whole pharmacokinetic aspect of the inhaled corticosteroids, whether they are intranasal or oral. On a theoretical basis -- well, actually it is a question. Is there any theoretical basis to presuppose that steroids that are given intranasally or by oral inhalation are actually more active than those given orally.

The reason why I am asking is because to a large extent there is no bypass through the liver with initial degradation. Have you looked at that at all?

DR. AFFRIME: Theoretically, I think, if it is absorbed through the pulmonary vasculature, perhaps if you go directly to the heart and then through circulation based anatomically, but we don't have any information on that.

DR. CARA: I would also like to hear Dr. Levine's comments in terms of use of the 250 microgram cosyntropin dose. I mean, that is kind of like hitting the pituitary with a sledge hammer and I don't think that it has the

sensitivity to really evaluate much renal suppression. I wonder if she would comment on that.

And, also, perhaps, on the length of suppression of the adrenal, how long does the adrenal take to recover from some of the suppressive effects of steroids?

DR. LEVINE: Well, I think, as I kind of might have led everyone to believe this morning, I think the 250 microgram ACTH stimulation is not sensitive so that I think it is using a much too large a dose. I am hopeful that using the low dose might be a more sensitive test for what are probably subtle suppression of the hypothalamic pituitary adrenal axis. But we don't, obviously, have enough data, but I would think that that is something that should be looked into.

In terms of how long does the suppression last, it is really very, very variable depending upon the degree of suppression, how long it has been going on. There certainly are individual variations and it may take months before there is complete recovery of the axis from suppression. so, it is, again, very variable depending on a lot of factors.

DR. LI: A summary comment at this point might be that the study that we just saw apparently shows an effect of intranasal beclomethasone on growth velocity in the absence of documented measurable bioavailability and in the

absence of a measured effect on the HPA axis. There would be at least two theoretical situations when that might occur. One, at least with the HPA axis, one possibility is that intranasal beclomethasone, in fact, does affect the HPA access, except it just wasn't measured in this particular study with this particular methodology.

The other possibility is that the effect on growth can occur in the absence of effect on the HPA axis. Is that correct, as a possibility, Dr. Levine?

DR. LEVINE: I think that is a possibility and I think until we have much better data on how much -- on whether there is suppression, how frequent it is and so on, we won't know that answer, but it is certainly possible.

DR. LI: And we also learned that the effect on growth might occur even with undetectable drug and circulation, which is amazing if you think about it.

DR. KELLY: That was undetectable in adult normal volunteers versus the kids who got the detectable --

DR. LI: That is correct. I realize that. The pharmacokinetics weren't done in children and also as Dr. Baraniuk said, were not done in children with allergic rhinitis.

Dr. New, did --

DR. GROSS: Can I make a comment about that?

DR. LI: Yes, please.

DR. GROSS: I am not sure that it is actually correct to say that you can have a large biological effect without detectable drug in the blood. I mean, a drug can enter the blood, become attached to receptors and become undetectable within minutes, but the biological effect may remain for days or even weeks or months.

so, to me, it is not very convincing -- and correct me if you don't agree with this, but I am not sure that one can conclude simply from the fact that there was no detectable BDP in the blood that there wasn't a huge biological effect.

DR. BONE: Just to pursue that a little bit further, what was the limitive quantitation of your assay? Was it --

DR. AFFRIME: It was 50 gigarents(?) per ml for BDP and 17 and 21 and beclo was a hundred.

DR. BONE: What is the relative potency to hydrocortisone? Somebody can multiply out what that equivalent would be.

DR. AFFRIME: I can't answer that baseline.

DR. BONE: Maybe after the intermission we can have that figured out.

DR. LI: Dr. New, did you have a question you wanted to ask?

DR. NEW: I must say that I am a little confused.

1 understand from the previous presentation that oral prednisone with or without the inhaled steroids did not affect growth. Prednisone is readily absorbed. Its half life is longer than that of hydrocortisone. And I really don't know what its half life and potency is relative to the inhaled steroids if they ever appear in the serum.

I mean, apart from the affinities in the binding, the question is if they are not there, how can you measure it? So, I am very confused about that.

DR. AFFRIME: I was confused about those data as well, but in our study -- the 10 milligram dose is a small dose daily. Pharmacokinetically, at the end of the dosing interval it is barely detectable and we did see an effect on HPA axis in that study.

DR. LI: One last question from Dr. Osborne.

DR. OSBORNE: I realize this might not be a very useful question but could the degree of inflammation either in the nasal mucosa or in the lower airways affect the amount of absorption and are there any studies to help us along those lines to give us guidance?

DR. AFFRIME: I think it could, but I don't have any data to provide.

DR. LI: Okay. Thank you very much, Dr. Affrime, for your presentation. And I would like to thank all the sponsors for their careful presentation and willingness to

present.

We are running a little bit past time. I think we can take a reasonable break. We will resume promptly at 3:20.

[Brief recess.]

Agenda Item: Open Public Hearing

DR. LI: Ladies and gentlemen, we will begin the open public hearing part of our meeting today. I think we have had a very interesting morning and educational one. I appreciate the sponsors' willingness to give their presentations and I thought that was interesting for us.

In some ways, this section to me is the most exciting part of the day, partly because it is sometimes unpredictable . We have a number of individuals who have notified the committee about their willingness to speak on this subject and we have accommodated them all.

so, we have actually a very full schedule and in fairness to all the speakers, again, I would respectfully request that each of the persons speaking at this open public hearing keep strictly to their allotted time.

We will not have questions immediately after each of the presentations. So, one presentation will follow the other. If time remains at the end of all the presentations for questions or discussion within the committee, we will proceed with that.

The first speaker at this open public hearing is professor Tim Clark -- I would ask all the speakers at the open public hearing to please inform the committee of any affiliations they might have either academic, but particularly with industry, including any financial affiliation they might have, as well as information as to who paid their transportation to Washington.

so, our first speaker then is Professor Tim Clark from the National Heart and Lung Institute in London. Professor, welcome to Washington.

MR. MADOO: If I may interject as well, if you could also articulate whether or not you are receiving a fee for presenting itself.

DR. CLARK: No, not to my knowledge.

Professor Tim Clark. My fare was paid by Glaxo Wellcome. I am a consultant of -- do I get my five minutes after this because it might go on a bit. I have worked for a number of pharmaceutical companies over the years and within the last year I have also been on the International Advisory Board of Merck.

I have dealt with pharmaceutical companies as formerly dean of the National Heart and Lung Institute, securing institutional support for projects, programs and academic staff.

But my main reason being here is I am going to try

and set out in this very brief presentation and that is I have just been involved with the development of inhaled steroids for the last 25 years and I just couldn't miss this opportunity of speaking.

My last conflict of interest is that I am five foot seven, but I am proud of it. Actually, I am five foot six and a half. My mother put five foot seven on my passport application, so I may never get over that.

I would just like to spend the five minutes trying to put this problem as I see it in perspective because it has been a burning issue and, as Gail Shapiro put it, it has been a weight on our shoulders for the 25, 26 years, ever since inhaled corticosteroids were introduced.

And they will introduced, I will remind you, in 1972, and they were primarily introduced as a substitute for oral steroids. It was correctly assumed that their topical nature and the small dose delivered through the airway should limit the amount of systemic effect and, indeed, there is ample evidence that is the case.

The initial dose that was chosen for interesting reasons I won't bore you with, the 400 micrograms daily, was found to be effective. It had far less systemic activity than an equivalent dose of oral steroids, about 10 milligrams of prednisone per day. But even in the first days, in, 1973, I think it was, and Soren can correct me, I

think Nevils (?) Mooken (?) showed that using urinary cortisol studies that even 400 micrograms per day of BDP was associated with detectable systemic activity.

So, there is no doubt -- no one, I think, in their right mind would contest that some systemic activity can be observed even at these low doses. Systemic activity was found to be in this first decade inevitably more likely at higher doses and as one of the previous speakers has commented on, there is considerable inter-subject variation. So, some patients gain better effects from treatment and some show greater systemic absorption.

So, this subject of inter-subject variability is one that has bedeviled the investigations over the last 25 years. In the 1980s, it is important to realize that although the medication was introduced as a substitute for oral prednisone for severe asthma. Because of its undoubted effectiveness and its low level of systemic activity, as shown by many studies with BDP and then more recently with budesonide and other steroids, there was growing confidence about effectiveness and it began to be used in mild to moderate asthma.

Now, that was not the original intention, but clinicians increasingly used it and found it effective in mild to moderate asthma. From that very beginning, concerns were expressed by all of us who were involved in the initial

studies about the effects of systemic absorption.

One of the studies, which I am sure was discussed this morning, set up by Simon Godfrey at the Brompton(?) Hospital in the 1970s, was published by Balfoul (?) Lynn(?) in the journal showing final adult height in 60 asthmatic children, showing that those on inhaled corticosteroids did not seem to have any change in their final adult height.

Now, I am not putting this up as the definitive study. It clearly was not the definitive study because here we are still discussing it. But as long ago as the early 1980s, this issue was a problem and the fact it remains a problem after 25 years of intensive investigation suggests that we may have some difficulty ever coming to a final solution. But I think the discussion about methodology this morning and the advice given from our colleagues in endocrinology, I think, has been extremely helpful to those of us in pulmonary medicine, who have tried to make these assessments.

In the 1990s, the aim has been that the control of asthma should be the goal of therapy and over the eighties and nineties, the benefits of inhaled corticosteroids have become much clearer. I think this is the thing that concerns those of us who are adult pulmonologists. I cannot speak as a pediatrician, but the benefits that we see of less morbidity, the reduction in emergency room visits in

every study that has been published, the reduction in hospital admissions, the increased school attendance, a possibility of falling mortality, although that is an arguable point, and the cost effectiveness of inhaled corticosteroids has been attested by many studies in the last 10 to 15 years.

The loss of effectiveness from this medication if there were scares that it might be dangerous and it would not be used would have a very significant effect, I think, on the morbidity of patients with asthma. So, we have the position in summary that higher doses are less systemic in oral steroids and we should, therefore, try and, as people have said before, titrate the dose of treatment according to the need. Those with severe asthma will have higher doses because they are less systemic than oral steroids, but in all patients, all clinicians try and find the minimal effective clinical dose.

That may not be the same as the minimal effective dose you are asking for for labeling. But for clinical purposes, the minimum effective dose is sought and at low doses, the side effects from systemic absorption appear to be minimal and these low doses can achieve considerable improvements in morbidity and the cost to the health care system by reductions in expensive visits to emergency rooms and to hospitals.

It is one of those situations where it is a win-win situation. The patient is better and the health costs are reduced and insurance companies are happy. So, low doses of inhaled corticosteroids are consistent with good control of asthma and patient satisfaction.

If there is public anxiety because there is public anxiety and in the USA I am told that cortico phobia is still very rampant, that if there is public anxiety, my concern is that this will lead to the use of a very effective treatment that is promoted by another agency of the Federal Government through the expert panel review and the guidelines of NHLBI and the fallen use will lead to poor control, increased morbidity, increased exacerbation rate and if it is true that poor asthma stunts growth, it will lead to a reduction in growth.

so, on balance, having seen this problem over a 25 year period, I would commend that you remember the benefits of inhaled corticosteroids and be absolutely certain that the effect on final attained height is going to be detrimental to the patients. Unless you are certain of that, I think you must be very careful in how you label this.

Thank you.

[Applause.]

DR. LI: Thank you very much, Professor Clark.

'Our next speaker is Professor Pedersen, who we have heard from before briefly. If you wouldn't mind, please make a brief possible conflict of interest statement and please be attentive to our schedule.

DR. PEDERSEN: I am a professor of pediatric respiratory medicine. I have been doing research of inhaled steroids. That has been our main research area for the last 15 years, the use of inhaled steroids in children. And I am here during my vacation because I felt this was quite important .

My expenses, hotel and travel, have been sponsored by Astra, Glaxo and Rhone Poulenc Rorer, in combination. so, they split the expenses so I could come here to speak about one of my very important research areas.

What I am going to do today is also like Professor Tim Clark, to share with you some of the experience we have with the use of inhaled steroids in children over the last 15 years in Denmark. And I am doing this because what I have realized -- I am old enough -- I haven't got into the fifties yet, but I am old enough to see that the disease we see in Denmark now of asthma is totally different among children. We don't see severe asthmatic children anymore.

It is very, very rare that we see moderate asthmatics . We mainly see mild asthmatics. And I believe, but cannot prove, that this has something to do with the

change in management strategy we have, which is so very different from the one that you apparently here in the states .

I am going to show you some data. I will discuss the clinical benefits and I will discuss growth mainly based on a long term study we have been doing in children.

The minimal effective dose has been discussed often during this meeting and I will just show you a dose response study we did in children with severe asthma three or four years ago. What we found -- this is just peak flow. Again, you see 100, 200 and 400 micrograms per day given for four weeks and very interestingly, we find that 100 microgram per day is very, very effective and we do not get on this parameter any additional improvement by 400 micrograms per day.

These findings are very important to remember when we discuss dosing and risk of adverse effects of inhaled steroids. It was the same with other outcomes but I must say that the control of asthma, exercise-induced asthma, required a somewhat higher dose. It required about 400 micrograms. This is not the only study. There have been several published studies, dose response studies and trials. This is a group parallel study and it shows the same thing, that 100 and 200 micrograms are very, very effective, better in this respect than placebo.

so, the main message is that low doses are very effective. This study was published in Archives of Disease in Childhood by -- in Respiratory Medicine by John Price(?) as the first author, and that was a comparison, but it is a group parallel study with fluticasone 50 microgram twice daily compared with sodium glomoglycades(?) 20 milligram four times a day. And in all of our parameters, this low dose was markedly more effective than to the treatment of sodium glomoglycade. And there have been seven other studies comparing these low doses of inhaled steroids with other NC(?) asthma treatments in patients with mild or moderate asthma and in all cases have these low doses been as effective as and in the majority of the trials more effective than the other treatments with which they have been compared.

so, this has been some of the background. While we have changed the strategy in Denmark, so now we use inhaled steroids as first line treatment for children with chronic asthma, who require continuous treatment. So, that is the first line treatment.

When this was introduced back in 1986, we decided that we wanted to do a long term follow-up to see what happened, whether our children would become dwarfs, what would happen with their bones. So, we did this study, which has been going on for 11 years now. And we have a cohort of

children and we follow their growth rate and their lung function during a run in period of at least one year, on average one and a half years.

They have come to our clinic at six month intervals during this period of time. At each time we measure their height, their lung function. We adjust their dose of inhaled steroids in the group, which receive inhaled steroids. At five year intervals, we do Dexa(?) scales to measure their bone mineral density and we also do other recordings like bronchial hyperactivity, et cetera.

The idea is to follow these children into adulthood. What I am going to show today is -- and I must say these are the two same doctors. They are stable in Denmark and it is the same two nurses doing all the measurements throughout this time. So, that is another advantage.

What we have here is not a blinded trial and it is not a randomized trial. What we wanted actually to do was to follow children once they were put on treatment, but either we were lucky or it turned out that some parents were very afraid of inhaled steroids. So, they decided to continue on treatment with other asthma drugs. I don't have time to give you all the baseline data here, but they are very comparable in disease severity.

This group has been expanded over time and a few

have dropped out of this for various reasons, which we may discuss afterwards. But what I am going to show you is some efficacy data and some safety data from this.

Just to reinforce what Professor Tim Clark said was that during run in the number of hospitalizations in the two groups were exactly the same. This group had not changed in their treatment, so they were still hospitalized three out of a hundred children were hospitalized with acute asthma every year. That was an 85 percent reduction in the children who received budesonide. This has been continued and we virtually don't see acute admissions anymore.

The second thing is that what was finding -- in accordance with what Gail Shapiro presented, that the children who had had asthma for a short period of time, the response was much better in the lung function than those who have had asthma for a long period of time, emphasizing that -- it is suggesting that we would get a better result with the inhaled steroids if we started those early rather than if we waited until the children have had asthma for a long period of time. That has been shown in four or five other trials now in adults and one in children that they have found similar things.

I am showing you here after four and a half years to see the lung function and you can see that the children

who have received inhaled steroids, they have normal lung function; whereas, the group that has not is about 7 percent lower in lung function than the group receiving inhaled corticosteroids .

This is the group who started steroids after five years of delay and this is the group of children who started within two years after the debut of their asthma. What we can is that still after five years, four and a half years treatment, the group who had delayed treatment of their asthma, their lung function did not catch up. So, they got up to the same level as the lung functions of those who started very early.

so, it suggests that some reversible airway change has taken place in the airways of these children that we could not repair. But what is interesting, I think, more interesting is when we follow on what steroid these had required, we turned out that those who started early, not only had they better lung function but they could be controlled on a lower accumulated dose of inhaled steroid over these four years.

so, this suggests that if you want to give low doses of inhaled steroid, you should start early because in the long run that will save you steroid. They can be controlled on lower doses.

Now, the growth rate over the first five years is

the same in the two groups. It is about 5.8 and 5.7 centimeters per year and this has done by linear regression and it includes both pubertal children and prepubertal children. We have separate analysis for these, but I don't have time to present it.

This slide you have seen already today and where we have the predicted height and the measured height and you can see that this is in 37 patients, where -- who have reached their final height. What I have also included here is the green dots because that is the siblings of some of the patients who have attained final height, calculated at mid-parental height.

And as you can see here is that the inhaled steroid, they attained final height. The siblings is no difference in expected final height and the controls either, So, we cannot find that these children are growth retarded. They attain their normal final height.

so, the question is why are Danish children not ending up as dwarfs because we would expect this based upon the studies we have seen here today. We have seen now that they attain final height and they do this to the same extent as their siblings, in spite of the fact that they have been treated for seven to eleven years with inhaled steroids.

I think that this has been discussed already, that there are many problems with extrapolating short term trials

to long term effects. There may be different effects in different age groups. We have mainly focused today on prepubertal children. It may be because growth is delayed -- because in real life we tailor the dose to severity and there may be tachyphylaxis(?) .

I will just show you what we can see in our study. This is the height standard deviation score defined as earlier said today in the two groups before and this is the time when switch over to the treatment. What you can see" is that during the first six months and twelve months, there is' actually a significant reduction in the increase in height standard deviation score. So, if we had done the study here, we would have concluded that inhaled steroids had a significant adverse effect on growth.

But because we have continued the study, we don't see this effect. Now , we have -- because we change the dose constantly in this trial, it is very difficult to make dose response studies but we have more than 4,ooo growth measurements. So, we have 4,000, six month growth intervals and we have divided changes in these six months in the height standard deviation scores according to dose during the previous six months.

You can see that in children receiving 400 microgram and less, there is no -- it is normal; whereas, there is a significant reduction in those receiving a higher

dose and in those -- we have very few who are receiving very high doses.

so, that shows and suggests that there is a dose response relationship and that low doses are not causing any adverse problems. What is interesting, I think, and perhaps surprising is that you see that lung function goes down with higher dose and that might be because that they are less well controlled. So, we don't know how that affects the growth of the asthma children, that they are poorly controlled and also they are less well controlled during the winter, where we know that they grow less.

so, it is very difficult to say whether this is the high doses or whether this is other factors and we cannot judge that based on our study.

We have divided the children into pubertal and prepubertal children. Those who receive more than 400 micrograms during the previous six months and what we find is that those during pubertal based on Tanner stages, they grow normally; whereas, those, the prepubertal, they were significantly reduced. This is the mean and the 95 percent confidence intervals for the changing high standard deviation score.

so, again, suggesting that there are different effects in different ages. We have also bone age and you can see that those who receive high dose, they have a lower

-- the bone age is also retarded in these groups; whereas, there is no retardation in the development of bone age in those receiving the lower doses compared with the control children.

If we do the same exercise as Rhone Poulenc Rorer did in their presentation, that is, adjust the development in height with the development in bone age, we see that it is very close to 1 and not significantly reduced, so suggesting that it may be growth delay rather than a growth stunting effect that we see that the children may grow longer.

so, I think that that may be some of the reasons. This is not proved, but I have taken it out to show that assessing these long term studies is very complex and we should be very cautious to make two big a conclusion based upon one year studies and extrapolate them to long term growth because there are different age groups. There are different doses than the ones used in these studies and also the effect on bones may balance the effect on height.

When I read the literature and you may agree and you probably disagree, I think that the conclusions, if we go out in the literature and look upon day-to-day clinical trials and growth, I know they are less well controlled and they are not up to the standard, but it is striking that the conclusions from these studies are quite different from

those of the very short term or one year study because they don't find the same effects on growth.

Those are huge studies. One is 3,500 children recently. There is our own study. There is a Finnish study on conscripts and they are very different from the short term findings. I think that in our hands and in Scandinavia, at least, low daily doses does not adversely effect growth. And I am talking about doses up to 200 micrograms, 400 perhaps per day. We mainly use budesonide and fluticasone.

Treatment with higher doses, they do reduce growth, but I think the vast evidence is in children age six to ten years and I think we need more studies in young children and in prepubertal children before we have the full picture and we can make firm conclusions and no studies have found an effect on final height, but, of course, the longer the study, the less controlled they are and the more they are open to criticism.

But I think that when labeling is done, it is very important to remember that clinical effects of the inhaled steroids and also the doses required to achieve this clinical effect and also that in day-to-day practice, it is possible to achieve very good clinical effect without detectable adverse effects on growth or on final height or -- and I can say this -- bone mineral density, but I haven't

shown you this data here.

Thank you very much for your attention.

[Applause.]

DR. LI: Thank you very much, Dr. Pedersen, for that illuminating presentation.

Next at the open public hearing is Dr. Brian Lipworth. Dr. Lipworth, if you are here, welcome. If you wouldn't mind opening with a brief conflict of interest statement and please proceed.

DR. LIPWORTH: I have nothing to acid to what the previous speakers have said, so I will just leave it at that. Thank you.

DR. LI: All right. Thank you.

Next we have Dr. Michael Newhouse, who has requested to address the committee. Dr. Newhouse.

DR. NEWHOUSE: Thank you.

By way of a conflict of interest statement, my expenses for coming to this meeting have been covered by Battelle and by Inhaled Therapeutics, where I am currently doing a sabbatical. I am clinical professor of medicine at McMaster University and director of the Aerosol Research Laboratory there that I founded about 25 years ago.

I would like to very strongly support what both Tim Clark and Soren Pedersen have said. I have had considerable experience in treating both adults and infants

and children for asthma with inhaled steroids and I am more than old enough to remember the days before we had these remarkable agents available when many of our patients had features of Cushing's syndrome, were losing height because they were collapsing their bones and where the situation for them was miserable and the treatment was almost as bad as the disease.

All of that was changed in a remarkable way when inhaled steroids came along and we have continued to get better and better steroids and better delivery systems. I suppose as part of my conflict of interest statement, I should mention I invented a device called the AeroChamber, which is a valve folding chamber that is used widely and that, too, has made it a lot easier to treat infants and children,

There are a number of these devices, some of them with mask attachments that make that very straightforward. I think the major problem in the United States is not the side effects of inhaled steroids, but rather the underutilization, as others have said. I think that needs to be emphasized again and again and again.

Compared to Canada per capita, inhaled steroids are used about a third as often in the United States. While I don't think this has been looked at really closely, I suspect that the result of that is that many of your

children are being undertreated, although it could be that you could take the position that ours are being overtreated.

I think the really important issues are to always stress to primary care physicians -- and I realize that as a secondary tertiary care specialist, I am only seeing the tip of the iceberg. The people that we must consider when writing any regulation, when educating colleagues are those that see probably 90 percent or more of all the patients. That is the people in general practice.

There is a great steroid phobia in the United States that has also been alluded to before that I think comes from a combination of the greater emphasis on side effects and therapeutic effects with inhaled steroids and I think in that regard, the press has amplified problems that are very small and, as so often happens, tend to concentrate on the evils rather than the benefits because that may sell papers or whatever.

But good news, I have been told by my friends who are journalists, good news is no news. So, the tendency is to stress the bad news and I think it very important as the FDA decides to try and put some of these things into context that the good news, which in this case is, I mean, from what we have heard so far, that the effects on growth are minimal and that we are, in a sense, almost talking about how many angels are there on the head of a pin because the amount of

change is so small, but if we compare that with the amount of benefit from inhaled steroids with regard to control of asthma that is massive, it is hoped that the material that finally comes out of the committee can reflect that tremendous benefit and the very, very small likelihood of side effects.

The other point I want to make is that the thing that inhaled steroids has done for us clinicians, it has made it a lot easier to train patients in the management of their disease and it has done that because you can virtually use monotherapy for the maintenance therapy of asthma. The only drug that I know of at the moment that you can do that with is inhaled steroid.

That is, you put children on a maintenance dose or adults, as the case may be. You put them on a maintenance dose, which you determine is the minimum maintenance dose when they are well and having determined that, you can double it or quadruple it for two weeks when they get a viral respiratory illness or if they suddenly get a cloud of allergen, walk into a houseful of cats or whatever.

So that they can fix themselves, simply adjusting one drug. Before that, it was polypharmacy. They were getting theophylline and they were using a lot of beta agonists and so on and so on. Obviously, they still need to use beta agonists for rescue but for chronic care, the

ability to just manipulate one drug makes it really easy to teach patients how to manage themselves.

Finally, there is no doubt that one never wants to use more of any drug than absolutely necessary. So, we should be using whatever tricks we can to achieve the minimum maintenance dose. I think those sorts of things include the question, is the drug that we are administering to the patient the drug that will give the least side effects, so that as we get newer and newer steroids, as clinicians, we are likely to be looking for the ones that are least likely to cause problems.

Secondly, is the optimum dose being used? And, again, that again is -- the point of that is to stress to clinicians that they must always be seeking the minimum maintenance dose and to teach patients how to do that by regular tapering.

The third thing is what about adjusting the physical characteristics of the aerosols and holding chambers have succeeded in doing that very well so that the total body dose can be reduced about 75 percent while targeting the lung with smaller particles that are perhaps more appropriate.

Then recently with the studies of Craft, et al., the question has been raised, are we targeting the right parts of' the lung anyway. Should we just be targeting as we

have in the past the larger and intermediary airways or is there a whole lot that is going on out at the alveolar level that we should be treating and it will be very interesting to see as we get smaller particle aerosols, whether those are more effective and cause fewer side effects because of the smaller doses that could be used.

Finally, there is an issue that I think needs addressing experimentally and one that I think many of us have observed and that is that in very young children, whose asthma is often due to respiratory syncytial virus, for instance, if you begin to treat them quite early and you bring them under really tight control, some of those infants and young children actually seem to get cured over time, over a year, a year and a half or two years and eventually come off systemic steroids altogether.

Now, this issue needs to be property resolved. There is a little bit of literature that suggests that that doesn't happen very much, but I don't think this question has been properly addressed. If that is the case, then we perhaps should be using larger doses early on, bringing these children under really good control and then holding them at a level of control and doing so for many months, perhaps until the airway heals, whatever that is.

But it is a question and I think we need to address because it could lead to more children getting

better.

I think that is really all I have to say and it just stresses what others really have said. Thank you very much.

[Applause.]

DR. LI: Thank you very much, Dr. Newhouse.

It so happens that we do have someone in general practice or family practice with us today and that would be Dr. Stuart Stoloff, who is our next scheduled speaker at the open public hearing.

Dr. Stoloff.

DR. STOLOFF: I am Stuart Stoloff. I am a family physician. My wife saw me sign the check. I am not being paid to come here. I have consulted for a number of the companies that are involved in these discussions.

I am a family physician. I am a solo practitioner for 20 years, same office. I wish I had had the same nurse for 20 years. I am a clinical associate professor of family community medicine at the University of Nevada School of Medicine.

My interest in pediatric allergy and asthma extends to the fact that I have been a member of the Expert Panel 2 for the National Heart, Lung and Blood for the guidelines. I have also been a member of the pediatric asthma writing committee on pediatric asthma, promoting the

best practice guide that Dr. Shapiro talked about.

I have also written extensively in the literature on pediatric asthma and allergy, as well as done educational films and lecture around the country.

Why I came today is because I am concerned as a primary care physician about the perspective of physicians who do what I do, especially with respect to steroid phobia, because from the patient and the family view, what I see everyday is steroids are anabolic steroids. Steroids are dangerous products and that is how the introduction occurs with the parent when they are discussing this matter with me on the care of their children.

The other issue is how do I educate the patient and the family in the time of an office visit? Can I change the behavior and the mind set. It can't be done right now with the time I have. So, if there is new product labeling, this matter will be by my perception worse and by my peers worse in primary care.

The new labeling effect on the physician, let alone the family, will be perceived as raising inappropriate concerns. If it wasn't there before, why is it there now? What aren't they telling us?

It will decrease the confidence in the clinicians in drugs' efficacy and safety across class. It will markedly decrease the physician's family discussions of the

benefit versus the harm of the medications and that will result in the one thing that none of us in this audience wants and that is a barrier to care.

The impact of the new labeling on the future care of pediatric allergy and asthma patients will. be a loss of confidence by public and physicians in the benefits of these drugs. There may be an erosion of control of the asthma and allergy and I think that will occur associated with a diminished quality of life for our patients.

The major issues to explore include the factors involved in poor asthma control, not just the medication we are giving, and these factors include how we word new labeling, the deficiency in the recognition of asthma severity by the patient and the family. That is a major factor. The perception of the patients and their family members is vastly different than the perception I developed in the questionnaires and the questions that I obtain from these people.

Associated with the potential for the new product labeling is suboptimal treatment, which is reduced compliance/adherence to the medications, both by the patient and the family and by physicians because right now, as was stated before, less than probably 5 percent of all primary care physicians in this country do stadiometric testing on their patients. And there are numerous reasons, as most of

us know.

There is an inadequate knowledge of understanding of the disease, including insufficient patient and caregiver communications at the present time, which will be unfortunately further enhanced by potential new labeling and the side effects of treatment or lack of treatment by lack of use of these appropriate medications is a major concern to me. The increased fear will result in increased loss of communication between the patient and the physician.

As one physician, when I discussed with them recently, a peer of mine in my town, said, listen, if I have got to talk anymore against what the person is saying I don't want, I will just give them something else. I don't have the time. That is what concerns me the most.

so, what we need to look at is a better way for a partnership within this labeling issue. We need to look at a better way to diminish the effect of the new labeling and not to raise the concerns and fears inappropriately of both the patients and the primary care physicians in this country and definitely not to create fear which increases barriers to care.

Asthma control is diminished by these barriers, we all know. Time increases need. Time increases problems with communication. And what primary care physicians in this country will tell you is time is not what they have.

They don't have time.

So, we have to figure out better ways to incorporate whatever you do in labeling to assist the physicians in this country, the primary care physicians, who take care of over two-thirds of these asthmatics in how they are going to educate their patients about the benefits versus the potential risks as they exist in what we don't know and what we do know.

The monitoring, that is another problem. We have to educate the physicians. I am all for improving methodology to educate physicians in monitoring for growth velocity.

And to end, the issues of steroid phobia, as a primary care physician, that I see are the fears and the misconceptions about inhaled corticosteroids today before you even finish your final discussion. What are the real untoward side effects? Have we even developed methodology to define them? Is there a reduction in efficacy over time? And how do we obtain a better communication between the physician and the patients they care for?

Thank you.

[Applause.]

DR. LI: Thank you very much, Dr. Stoloff.

Our next speaker is Ms. Nancy Sander, who is president of Allergy and Asthma Network/Mothers of

Asthmatics.

Ms. Sander.

MS. SANDER: Thank you very much.

First, as a parent and a patient advocate, I want to thank Stuart for his great comments just before mine. I am Nancy Sander. I am president of the patient education and advocacy organization, the Allergy and Asthma Network and Mothers of Asthmatics, Incorporated.

We gratefully received funding for educational programs and/or research from each of the pharmaceutical companies, whose products have been represented here today. However, I am here on my own time, representing the views of patients.

My comments reflect experience as a patient advocate, a researcher into the behaviors and outcomes of patients with asthma and as a member of the coordinating committee of the National Asthma Education and Prevention Program since its inception.

I have asthma, as do three of my four children. I am not, however, an allergist, a pulmonologist, a family physician or an endocrinologist. Therefore, as you have investigated these issues today, I have listened very carefully. For over 12 years, my daughter has required daily high doses of both intranasal and inhaled corticosteroids, also with periodic bursts of oral

prednisone to manage her asthma, her rhinitis and her chronic sinusitis.

But prior to the topical corticosteroids, she also was requiring nearly daily doses of prednisone. Now , she is 19 years old and I am very happy to say she is 5 foot 7 and she wears a size 10 shoe. Now , as a parent considering the questions before the advisory committee today, I wonder if anyone knows just how tall she would have become if she didn't require all these corticosteroids.

Then I remember that what might have been is not nearly as important as what is real and that is that she is alive and here with me today.

During my pregnancy with my son, Joey, however, I was taking theophylline. During that time I was diagnosed with -- we were diagnosed with intrauterine growth retardation and he was born early and very small. He has a very mild form of asthma but he has never been on inhaled corticosteroids and 17 years later, he hopes to achieve his sister's height someday.

Now, both my son and daughter experienced factors affecting growth with very different outcomes and despite best efforts, experts have never been able to give me any clear answer for those differences. But looking at this subject from my perspective alone, it can never represent the views of patients as a whole. The breathing and growing

doesn't happen to patients as a whole. It happens to families, to individuals, just like mine.

That is why as an organization, we focus on conducting research with families to learn more about how the disease and its management affects or impacts the quality of families' lives. We know that families are concerned about the unwanted side effects of any medication used for a long time. I mean, any medication used for a long time, but particularly when that drug contains the word "steroid" within it.

You know, where do we find comfort as parents and as patients? Well, it is in documents such as the Expert Panel Report 2. It has saved the lives of millions of children, improves the quality of life of millions of children because of the countless references to the importance of the use of inhaled corticosteroids and the treatment of asthma today.

Of the 15 million people with asthma, one would think that if there was a problem with growth significant and that was related to the use of inhaled corticosteroids, that it was significant to warrant changes to labeling, the evidence would be more convincing or compelling. We would see support organizations sprouting up by now.

Now, you know, we produce a monthly newsletter, the Ma Report, and in addition we publish numerous books and

videos and other forms of literature for families with asthma . We also answer hundreds of letters and phone calls and e-mails each week. And these are questions that range from everything about inhaled corticosteroids and what they are doing to my child's eyeballs and to their -- or what will they do? What are these things, to, you know, questions about where they find mite proofing casings for bedding.

so, we are very familiar with the kinds of questions that patients ask. So, if this committee should find sufficient evidence to recommend a change in labeling, which I hope you don't, I urge you also, in addition to all the things that Stuart raised and Brenda Conner raised earlier today, I urge you also to provide guidance for how we can answer some questions that we are going to get, such as, well, at what point do you recommend evaluation by an endocrinologist of a child whose asthma and/or rhinitis requires daily use of topical corticosteroids?

How is the diagnosis of topical corticosteroid related growth problems made? Is stunted growth permanent? How much is enough medication to treat symptoms but not enough to slow or stunt growth? How often should a physician order a bone age or a bone density test?

Are females with milk intolerance, who also require daily topical steroids at greater risk for

osteoporosis? Will children be hurt more by labeling, which frightens their parents or by using the topical corticosteroid under the guidance of their specialist?

The questions could go on and on and on. I even got more questions today as I was sitting here listening. But, you know, the biggest question in my mind is what alternatives can we present to families that provides the same level of results of topical inhaled corticosteroids today. And I tell you I am so very thankful for the care that my daughter has received that includes the use of inhaled corticosteroids.

My family is fortunate to have the ongoing long term care of an excellent board certified allergist, Martha White, who has orchestrated my daughter's individualized treatment plans for over 13 years. But most patients don't have that similar access. I truly think that the reason why my daughter is achieving the kind of life that she has today is because of that ongoing comprehensive care, which includes the use of any medication or any test that she ever needs.

I heard Dr. Shapiro say earlier that it was a great weight that physicians have had over the years in prescribing inhaled corticosteroids because of the questions that were unanswered. It is a really great weight for a parent to give a child a pill with questions and, you know

what, sometimes you make the decision not to do something because your fear is so much bigger than your ability to find the answers to the questions.

I agree with Dr. Stoloff's position 100 percent in that this is not the time for change. Thank you.

[Applause.]

DR. LI: Thank you, Ms. Sander, for those insightful comments.

Other speakers can use that microphone in the middle of the room. Unless you have slides, you may not need to come to the podium, but you are welcome to.

Our next pair of speakers both are here on behalf of the American College of Chest Physicians and they are Dr. Bennie McWilliams and Dr. John Georgitis.

DR. MC WILLIAMS: Chairman Li, Chairman Bone, members of the committee, thank you for allowing me to come here. My expenses are being paid by the American College of Chest Physicians and I am not getting an honorarium and I am going to be very upset if Dr. Georgitis is.

I am Bennie McWilliams. I am currently a practicing pediatric pulmonologist in Austin, Texas and also a clinical associate professor at the University of New Mexico School of Medicine and a fellow of the American College of Chest Physicians.

Up until one month ago, I was an associate

professor of pediatrics at the University of New Mexico School of Medicine and the assistant director of the Pulmonary Critical Care Division.

Thank you for this opportunity to issue of inhaled steroids. There have been numerous studies already presented today demonstrating the efficacy and potential side effects of inhaled steroids and I wish to present some of my views based on these and other studies.

I did want to comment that just recently making the leap from academics into private practice, I greatly appreciated the comments that Dr. Stoloff made. I think they were very appropriate.

Inhaled steroids are the cornerstone of therapy in pediatric asthma and as a practicing pediatric pulmonologist, I have seen first hand the benefits of the use of inhaled corticosteroids in children. This is evidenced by recent guidelines both by the NIH and the international guidelines, such as the global initiative that stress the importance of this class of medications.

Many of my own patients have exhibited significant lung improvement, decreased health care utilization and improved quality of life as a result of treatment with inhaled steroids. Additionally, studies mentioned previously today suggest that the establishment of inhaled corticosteroid therapy early in the treatment of childhood

asthma will result in better long term function in children, in whose therapy was delayed.

This is very important because I also think of asthma as a long term disease and not just the immediate management . Conversely, as a pediatrician, I have concerns about the long term side effects of medications on growing children. The long term effects of medications, whether they be beneficial or adverse, may not be evident for years. This is especially true of the potential side effects of the inhaled steroids.

Conversely, as was shown today, there is literature demonstrating delayed growth in children with poorly controlled asthma. As we have also seen today, the literature on the effects of inhaled steroids is mixed. However, the clinical implications of these changes, as we have said, were not clear.

Probably the best way to answer these questions are by long term studies. Dr. Pedersen has mentioned some of the international studies. One such study going on in the United States is the Childhood Asthma Management Program or CAMP and this is an NIH-funded study that is currently being conducted at eight centers around the country.

I was the principal investigator at the Albuquerque center until I left Albuquerque a month ago and remain an investigator in this study. This study is

following over a thousand children with moderate persistent asthma for approximately five years and it is scheduled to end at the end of 1999.

Numerous studies of growth and steroids effects are being followed in this study and, hopefully, at the end of this study many of the questions that we are addressing today will be answered.

so, in summary, I have seen first hand the beneficial effects of inhaled steroids in children with asthma and I look forward to the results of long term studies that should provide the answers to a number of the questions concerning all of us today. However, it is important to emphasize that the benefits of inhaled corticosteroids in pediatric asthma and recommendations resulting from this meeting should enhance the appropriate use of this class of medications rather than risks decreasing their use.

Thank you.

[Applause.]

DR. GEORGITIS: No, I am not getting any honorarium, Jim.

Thank you very much for the opportunity to address the advisory boards, as well as the FDA and the public. I am John Georgitis. I am a professor of pediatrics at Wake Forest University School of Medicine. I am the section

chief of the allergy, immunology and pediatric respiratory medicine.

I am a member of the board of regents of the American College of Chest Physicians and also a fellow of the ACCP, a medical society of more than 15,500 physicians, scientists, educators and allied health professionals, who specialize in cardiopulmonary health, as well as critical care medicine worldwide.

I speak on behalf of the ACCP today.

The issues of corticosteroids in children is of critical importance for physicians and the public. As the current chair of the ACCP Health and Science Policy Committee, our task is to provide evidence-based guidelines for the practicing physician, which include pulmonologists, allergists, cardiologists, intensivists and cardiothoracic surgeons. We as a committee recognize the importance of corticosteroids in chest diseases and, therefore, convened an expert panel of physicians and epidemiologists to review the current literature for adverse effects of corticosteroids.

This panel is engaged in evidence-based grading of these publications and plans to write an applicable guideline for practitioners, hopefully, by the end of this year. The publicity of growth velocity suppression as it relates to the use of inhaled corticosteroids has created an

area of concern for patients and physicians. It is important that we evaluate all the facts, rather than single issues . It is also important to utilize evidence-based grading of the literature before establishment of clinical practice guidelines for practicing physicians and before instructions are distributed to patients.

As we all know, the morbidity and mortality of asthma is increasing nationally and worldwide despite great strides into the research, the pathophysiology and the chronicity of asthma. We do know that inhaled corticosteroids alter the course of asthma when used early rather than late in the disease process.

Instead of focusing on growth velocity suppression issue, we need to bring to the public eye our concern about the seriousness of asthma, its chronic nature and how it affects the quality of our patients' lives. For physicians treating asthmatic children, we need to provide criteria for monitoring patients for adverse effects of all asthma medications.

In place of debating the possible negative effects of inhaled and nasal corticosteroids, we need to educate the public and our patients about asthma and rhinitis, the role of environmental pollutants, tobacco smoke exposure and allergens, which cause and worsen these conditions. Currently, second hand tobacco smoke exposure has been

reported in greater than 40 percent of homes where an asthmatic child lives.

Do we need to scare our patients' families by focusing on the possible growth effects with corticosteroids rather than emphasizing the removal of tobacco smoke from the household environment?

Equally as important, our patients and public need to know about control of medications for asthma and rhinitis. They need to know about the deleterious effects of excessive reliance on beta agonists for asthma symptom control. Loss of productivity from the work force, school day absenteeism due to asthma exacerbations and poor control of asthma account in general for a greater percentage of loss in quality of life and productivity than do the deleterious effects of inhaled or nasal corticosteroids.

Consequently, we strongly recommend the importance of anti-inflammatory therapy as an acceptable treatment in controlling asthma be the focus and that this be brought to the forefront through asthma education of physicians, patients and the public.

Thank you.

[Applause.]

DR. LI: Thank you very much, Dr. McWilliams and Dr. Georgitis, for both your comments.

Our next speaker at the open public hearing is Dr.

Robert Miles, who is president-elect and presenting on behalf of the American College of Allergy, Asthma and Immunology.

Dr. Miles.

DR. MILES: Thank you. I am hoping I am going to be funded by the American College, but it was not agreed upon.

The American College of Allergy, Asthma and Immunology commends the FDA and these committees on addressing the issue of inhaled glucocorticoids in growth in children. In the U.S., Asthma cases have doubled in the past two decades. The CDC estimates that there were 6.8 million cases in 1980 and today there are 15 million. The number of asthma deaths have increased and continue to increase. The number of hospitalizations and office visits for asthma have also been increasing.

The greatest increase in the number of cases of asthma, as well as the greatest number of deaths, have been in the age group 5 to 14 years of age. There has been a 74 percent increase in asthma in the 5 to 14 age group and there has been 160 percent increase in asthma in the preschool children between 1980 and 1994.

In 1997, NAEPP Expert Panel Report 2 on guidelines for diagnosis and management of asthma, places major emphasis on the use of anti-inflammatory agents for mild

persistent, moderate and severe persistent asthma. Indeed, through the judicious use of inhaled corticosteroids, we have been able to taper many chronic steroid-dependent asthmatic youngsters off of systemic steroids and at the same time maintain excellent control of their asthma.

For others, the use of inhaled glucocorticoids have changed youngsters' lives from sickly, sedentary individuals to active, productive young people, who are physically able to successfully compete with their peers.

Allergic rhinitis cases have also increased. It is stated that 73 to 78 percent of asthmatic children have allergic rhinitis symptoms also. Many studies have shown that the use of intranasal corticosteroids can have a beneficial effect on lower respiratory symptoms. Allergic rhinitis and rhinosinusitis contribute to a staggering numbers of days lost from school and work.

Anti-inflammatory agents have helped to decrease the severity of these symptoms. We recognize that the risk of inhaled intranasal glucocorticoids and inhaled glucocorticoids and we attempt to taper the maintenance dose to the lowest possible dose to control symptoms, thus avoiding as many potential side effects as possible.

All of us in this room know that the risk from inhaled and intranasal glucocorticoids is minimal when compared to the devastating side effects of long term

systemic glucocorticoids. We ask only that the FDA and these committees move slowly and cautiously in. decisions concerning inhaled and intranasal glucocorticoids.

Please, do not set back the treatment of asthma 25 years by creating a repeat wave of steroid phobia and hysteria. The children and teenagers who need control of their airway inflammation the most may become victims of their parents' or even their fear of steroids.

In summary, inhaled glucocorticoids have changed the lives of millions of asthmatics for the better. The rule of reason should apply in this discussion and this decision. The benefit of inhaled and intranasal glucocorticoids in control of inflammation of the airways far outweighs the risk of side effects.

The risk becomes even less when the use of inhaled and intranasal glucocorticoids is monitored by those experienced in the treatment of asthma and allergic disease.

I thank you for your time.

[Applause.]

DR. LI: Thank you very much, Dr. Miles.

Our next speaker is Dr. Michael Welch and he is presenting on behalf of the Executive Committee of the Section of Allergy and Immunology of the American Academy of Pediatrics .

Dr. Welch.

DR. WELCH: Actually, I come today -- my name is Michael Welch -- I come today wearing a number of hats. The first hat is I must say I am a supported consultant for RPR for this meeting. But I wear a couple of other hats that I think are very important hats in front of you today. One is I actually as a clinical research investigator was involved -- in a part of a research group that I am a member of was involved in all clinical research growth studies that you saw today. So, this data is very dear to my heart.

The third reason is that I am representing the Section on Allergy and Immunology of the American Academy of Pediatrics . When we heard of this meeting and the possibilities of some new stronger language regarding this drug class, this is the kind of concern that the Section members and the Executive Committee had. This is the view of what we thought the mothers were going to now have and the pediatricians treating kids with asthma if we weren't careful with the kind of language that would come out of the meeting today.

so, the committee, the Executive Committee of the Section has prepared a statement that I am going to read to try to make sure that we come out of this two day session with some reasonable recommendations.

The Section on Allergy and Immunology of the AAP is the largest group -- and, by the way, I must say this has

been endorsed only by the Executive Committee, this statement, and there is a long process in getting this approved by the entire American Academy of Pediatrics. That has not -- this statement has not been sanctioned or endorsed by that larger group.

The Section on Allergy and Immunology of the AAP is the largest group of pediatric allergists in the country and as specialist in this area, we are involved in the treatment of tens of thousands of children with asthma and allergic rhinitis. Therefore, we have a special interest in the issue of possible growth suppression with the use of inhaled corticosteroids for allergic disease and any labeling changes that may occur with this drug category.

There is now considerable published data demonstrating beclomethasone treatment, as well as budesonide therapy, can cause small but significant slowing of growth in patients with mild or moderately severe asthma even at usual recommended doses.

Less information is known about the other three inhaled steroid agents, triamcinolone, flunisolide and fluticasone, but based on individual adverse medication reports, such as MedWatch, published case reports, growth suppression trends in underpowered published reports and theoretical considerations, growth suppression with these other oral inhaled steroid preparations is likely.

The five presently available inhaled formulations already contain a warning in their package insert about the potential retardation in children when using thee medications, but the language and strength of this warning varies between products. The Executive Committee is aware that the FDA is proposing class labeling of this category of asthma medication with uniform precautions for all of the oral inhaled steroid products.

Given the accumulated evidence that now exists with oral inhaled steroids and growth suppression, we feel this kind of precautionary labeling appears reasonable. While cautioning about the possibility of growth suppression, the FDA, in their new warning label, at the same time has appropriately pointed out that one needs to weight the potential benefits against the potential risks that long term growth effects are unknown, including the potential for catch up growth, and that children should always be treated with the lowest effective dose. The Executive Committee, therefore, agrees with the class labeling and the language being proposed for such labeling.

Now, information about the effects of intranasal inhaled steroid therapy and growth in children is much more limited than with oral inhaled steroids. The few studies done to date have been mixed in their results about suppression of growth. It is known that intranasal inhaled

steroid preparations are systemically absorbed to variable degrees, but the doses used for rhinitis given intranasally are in a range at least half that of oral inhaled steroids, making growth suppression less likely.

Furthermore, there are numerous differences between the various intranasal formulations, including strength, the vehicle and the recommended dose, making an entire class labeling of the available intranasal inhaled steroid preparations difficult.

The Executive Committee, therefore, feels that until further information is obtained from carefully conducted studies of growth effects of all the different intranasal inhaled corticosteroids, a class warning for this category of medication is premature.

Physicians, especially primary care physicians, have always been fearful of inhaled corticosteroid therapy in children. It has taken a considerable amount of time and education since the first introduction of inhaled steroids to convince primary care physicians to prescribe inhaled steroids for children with asthma and allergic disease.

Although inroads have been made, prescription data from the National Disease and Therapeutic Index, date that you provided, for the period of 1993 to 1998 indicate that only 9 percent of all inhaled steroid prescriptions written for asthma and 12 percent for allergic rhinitis are for

children under the age of 12 years.

Given the proven efficacy of inhaled steroids in these two diseases and the new 1997 NHLBI guidelines, which recommend inhaled steroid for all degrees of persistent asthma, theses percentages seem inappropriately low and suggest children with asthma are undertreated.

As the FDA gets ready to bolster the level of caution associated with inhaled steroid use due to a new appreciation of inhaled steroid's potential to cause small but significant growth suppression, it needs to be careful to avoid creating an intentional state of steroid phobia that used to exist and still exists to a certain extent amongst both physicians and patients.

Instead, the treating practitioner should take advantage of this highly effective form of asthma and rhinitis therapy, but while doing so, the physician needs to adhere to the following items in order to minimize potential adverse effects in patients on chronic therapy.

No. 1, monitor linear growth carefully. A three to four month interval between measurements is reasonable. A reliable and quality stadiometer unit that is calibrated regularly should be used and a person trained in doing stadiometry should conduct the measurements. The growth data should be plotted on a growth chart to be able to note any drop-off trend.

No. 2, the physician should titrate the inhaled steroid dose to the minimum level that controls the disease. There may be even certain children who can actually discontinue therapy for a number of months, such as during the summer, to be restarted at a later time, when indicated, based on symptoms and lung function.

No. 3, the physician should be aware that topical corticosteroids given by multiple different routes, including oral inhaled, nasal inhaled and dermatological preparations in a given patient may have an additive effect and increase their overall systemic exposure to corticosteroids and thereby their effect on growth. In other words, the total dose being used by the patient should always be kept in mind.

No. 4, the physician needs to be on the lookout for certain patients, who have greater than normal sensitivity to the systemic effects of inhaled steroids. These patients, when placed on inhaled steroids, can have quick weight gain, growth suppression and even sometimes Cushingnoid changes that indicate the patient has either an abnormal metabolism of corticosteroids or an unusual end-organ sensitivity to the small amounts of corticosteroid available systemically with all inhaled steroid preparations.

Finally, No. 5, non-pharmacologic approaches, such

as allergen avoidance, immunotherapy, should always be explored and implemented as adjunctive therapy to help control airway inflammation so that the lowest dose possible of inhaled corticosteroid therapy can be used in a given patient.

Thank you

[Applause.]

DR. LI: Thank you, Dr. Welch, for sharing those comments.

We have Dr. Philip Hopewell next, presenting on behalf of the American Thoracic Society. Dr. Hopewell, please include a conflict of interest statement.

DR. HOPEWELL: Thank you.

I have no conflicts of interest that I am aware of. My expenses are being paid by the American Thoracic Society and I don't do research in this area, which may minimize the effect of any comments I might make. I am receiving no honorarium unless I can interest somebody in the next few minutes.

Let me first of all issue a disclaimer. I am an adult pulmonologist without special expertise in asthma. I am, however, past president of the American Thoracic Society and have been put in the position of presenting a synthesized, consolidated opinion from our assemblies on pediatrics and on allergy, immunology and inflammation to

respond to the questions that have been raised by the advisory committee.

I would like to emphasize that the American Thoracic Society and those two groups within it that I just mentioned are particularly interested in this issue and are anxious to continue to be involved with the process as it moves through the FDA.

Today I would like to offer brief comments on the questions that the committee asked us to consider. These comments, as I said, represent a fairly summary statement from expert members of our organization.

First, the American Thoracic Society feels that patients and in the case of children, their parents or guardians have the right to know all the potential health effects of the drugs they take. We believe in the case of inhaled corticosteroids that there is sufficient evidence of altered growth in children to prompt a class labeling for all intranasal and orally inhaled corticosteroids by the FDA .

I would like to emphasize however, as other speakers have, that when used properly, these drugs are safe and effective and the risk for growth alterations are greatly outweighed by the benefits of these agents for children's moderate to severe asthma. The risks of overuse of inhaled and intranasal steroids by practitioners

unfamiliar with them is real, however, and proper labeling would help alert practitioners of the need for close monitoring and supervision of pediatric patients receiving these drugs.

At this point, the evidence supports only a warning of potential growth retardation. While we would support a change in labeling, we would oppose any changes that would limit the availability of corticosteroids to patients with lung disease and to the physicians that prescribed them.

Studies of nebulae steroids are in progress in this country and the ATS agrees that careful monitoring of the growth effects of these drugs must be included in these studies of younger pediatric populations. The studies are badly needed to provide the benefits of inhaled corticosteroids to younger pediatric populations, while at the same time providing important safety data.

Second, the ATS supports the need for lowest effective dose studies to be conducted on all new corticosteroid preparations seeking FDA approval. We also feel that the FDA should develop a strategy for developing lowest effective dose studies for currently approved corticosteroids. It is vital that these studies be conducted for all patient populations that are currently receiving corticosteroids, including prepubertal children

and adolescents.

Third, the ATS supports the need for. growth studies using new and existing corticosteroids. The ATS supports careful Phase 4 studies of approved corticosteroids, particularly those approved for use in younger populations to document the side effects of these drugs in routine clinical use, particularly with regard to growth, adrenal suppression and long term clinical effects.

The ATS recognizes the lowest effective dose and growth studies will place an additional responsibility on pharmaceutical companies. We strongly urge the FDA to work with the pharmaceutical manufacturers and the physician community to develop a reasonable time table and methodologies to initiate and complete these studies.

Finally, there are several important considerations in developing useful growth studies. The Pediatrics Assembly and the Allergy and Immunology Assembly of the American Thoracic Society will provide more detailed comments in the near future with regard to the duration of follow-up studies and technical considerations, such as height measurements and assessments of the effectiveness of inhaled corticosteroids in younger populations to supplement the comments provided today.

On behalf of the American Thoracic Society, I would like to thank you for the opportunity to comment on

these proposed changes.

Thank you very much.

[Applause.]

DR. LI: Thank you for your comments, Dr. Hopewell.

Next, speaking at the open public hearing is Dr. James Kemp, who is speaking on behalf of the American Academy of Allergy, Asthma and Immunology.

Dr. Kemp.

DR. KEMP: Thank you, Jim, and thank you for getting my name correct. I think my two adult children got Dr. Keep in there, so I am glad you were able to get it correctly.

I am perhaps so conflicted that it would be shorter if I just named the companies for which I have no conflict. My way is being paid by the American Academy of Allergy and I do want to speak regarding the position statement.

The Academy of Allergy is a specialty group that represents doctors and allied health care members, who really are very, very interested, almost exclusively to the diseases that we are talking about today. So, it is very appropriate that we have a position statement to make on the issues .

However, one of the advantages or disadvantages in

being the last speaker of the day is that much of what we would have said has already been said. So, I think in the sense of time, we will just actually review very briefly our position on this because a lot of what has been said is our position also.

The mission of the academy is to treat patients with allergic disease and to teach as well as to educate the public. We feel very strongly that the decisions about intranasal and inhaled corticosteroids should be made on scientific data and not on incomplete data that we feel is available in the literature and that has been discussed today.

We feel that the scientific information should reflect each corticosteroid, each dose of the corticosteroid, the formulation of the corticosteroid and the duration of which these steroids are used because, obviously, all of this can affect the response on growth or any other aspects of body function.

Why do we feel this way? Well, first of all, we have to look at our these drugs really the same because I think it is quite clear that not only are the drugs different, they have different molecular structures. They have different metabolizes, some which may be active and others inactive.

They have different biological half lives and

binding affinities for various receptors. The doses vary. They are not bioequivalent. They vary all over the place. The formulations are different. So, let's remember that we are not just talking about a class of corticosteroids. We are talking about drugs that are formulated very, very differently; some in dry powder formulations, some in metered dose inhalers, some in aqueous and even all the dry powder inhalers tend to be different.

So, to have a class labeling seems to be to us too general, too broad and perhaps too premature. Even the delivery systems actually determine how much is deposited on the nose or in the lung and depending upon the topical deposition that may very well affect the systemic absorption and the systemic side effect of these particular preparations .

So, I would plead with you not to think of them as just drugs in a class, that they are drugs in a class with multiple formulations and multiple differences.

In addition to the differences in the drugs and the formulations, there are a lot of differences in the way these drugs are used. They are either used alone or together, as my associate, Dr. Welch said. And perhaps there is some concern in using an intranasal and an inhaled asthma steroid, data which there is none. That is something we need to know.

They are certainly used in different doses, as I said before. They are used in different degrees of airway obstruction. I think it makes sense that an airway that is open in a milder asthmatic may very well receive more of the drug into the lung and, therefore, more systemic absorption than in a patient who is more obstructed or perhaps airway inflammation is a confounding factor in something that really relates to the degree of systemic absorption. And of this, we know nothing and, yet, there seems to be this need to perhaps get this information out and I understand that, but I think we shouldn't become too general in our approach.

Many different ages of children and adults use these drugs and they use them as has been discussed today for many different periods of time. Unfortunately, all of this, I believe, has raised more questions than it has answered and I think the biggest job of this committee is to give us some ways to get these answers.

What are the steroids that cause these effects? And what are the metabolizes and what are the safe doses that we can use? In essence, what is the minimally effective dose, something that has come up over and over here that I think we really must address.

And how long before these effects occur? What patients, if any, are more susceptible? And as I indicated before, how additive are intranasal and inhaled

corticosteroids? And the other thing that I think we need to know, are these effects on growth markers for other more serious systemic effects, something that isn't going to be addressed today, but is part of the ongoing story as we want to use these drugs correctly in our patients.

As you have heard over and over again, and I certainly do want to emphasize, we must look at the consequences of these diseases untreated with these very important agents, as well as the side effects that they may produce in a few patients, side effects which may or may not have any great consequence in the overall scheme of things.

You have also heard about steroid phobia and I don't want to spend a lot of time on that, but very obviously class labeling, I think, will lead to more steroid phobia unless it is very, very specific. If we don't talk about doses, if we don't talk about durations, if we don't talk about particular drugs, I think there may be a tendency to overreact to a class labeling, which will, obviously, lead to underutilization, which will, obviously, lead to increased cost, as well as morbidity and mortality.

This will just tend to reverse trends that have been established by the asthma guidelines. I really, as I indicated before, do not believe that the data that I have read in the literature, that I have even heard presented today, is general and broad enough to establish a class

labeling for all corticosteroids, all formulations of those steroids, all doses of those steroids in those formulations and all patients and for all periods of time.

So, if the guidelines are changed and developed, I do think that these parameters need to be taken into account and the prescribing physician and the parent and the patient be given as much specific information as they can. They might say, well, this is going to take too long and we don't have enough, you know, paper on the package insert, but I noticed in the proposed guideline changes that in three separate places precautions about growth are going to be mentioned if you agree with what has been proposed,

It will be mentioned in the "Precautions" section. It will be mentioned in the "Pediatric Use" section. It will be mentioned in the "Adverse Reaction" section. Perhaps a little too much for something that we are just basically learning about.

So, basically, we know these drugs are important. We know they have side effects when used inappropriately and in high doses. But we do also believe that there is a therapeutic index where the risk benefit ratio is the important thing to consider.

Now, just give me, Jim, if you can five seconds more as a pediatric allergist to make some personal comments without, hopefully, dragging this meeting out too long.

I personally want to thank Dr. Jenkins for bringing this issue to this meeting. In general, I come to these meetings because I learn a lot and I have ways of sharing and having you share with me information. So, I usually leave here much more enriched than when I came.

There is a red flag and I think Dr. Jenkins has brought this out and I think there is data that we have seen today that is now behind the wall, has gotten out into the public domain. I think some of this data has not been so accessible to us before and for that I thank him.

I certainly think we have had a lot of opinions about what is right and what is wrong and what is best and what is not best. And that is part of the American system. so, I applaud that also.

But I think there is a danger in going too far and if we go too far, we will do the wrong thing. So, I, once again, have some personal words of caution. And it does depend a little bit about how we look at the data. It is very interesting sitting out there in the audience either behind certain companies or certain people and watching their heads shake back and forth as they agree or disagree and a lot of times the agreement and disagreement is not so very consistent.

so, we have to remember where we are coming from when we look at the data and when we look at this picture.

And let's do look at the entire picture. And we do need more data. We do need to find the minimally effective dose. We need to look at the clinical relevance and not just the statistical numbers that are being presented to us today.

And we must have a level playing field, where we are measuring with the same ruler that has the same marker, these parameters that we are so concerned about. And I would certainly think that the guidelines -- and I am sure the Agency will do this -- will make this fair and when companies have no data because they have not done the studies, they should not be given an advantage over those companies that did do studies that give us the information that we have today.

so, let's make the level playing field appropriate. We have come a long way since 1900s when we thought that arsenic was the best treatment for asthma. Yet, we are still learning and even after a drug has been approved by the FDA by taking all these very simple and even complicated steps to get to this approval, we need to move forward with further information and I think that information will be forthcoming from this meeting and some of the recommendations that you will make.

However, I would suggest that you be careful and not take the clock backwards and create a problem by perhaps causing too much alarm. I know that is not the intent of

Dr. Jenkins or this division, but there is the press and there are other things that can happen to perhaps take this out of proportion.

In closing, I would just like to repeat something that David Allen said at the early part of the meeting. And he raised a question which said do inhaled steroids affect growth, and he answered this question by saying, it depends. It depends. And that is what we have to keep in our minds as you make the decision tomorrow.

Thank you very much.

[Applause.]

DR. LI: Thank you very much, Dr. Kemp, and I would also like to thank all the scheduled speakers who participated at the open public hearing.

At this time, I would like to invite anyone in the audience or anyone here today, who would like to address the committee.

All right. Our meeting is really scheduled until 5 o'clock, but it is really five minutes to 5:00 right now. so, I think I would like to close and adjourn the meeting for tonight, rather than spend five minutes on questions and answers.

so, thank you for coming. We will resume the meeting tomorrow at 8 o'clock in this room.

MR. MADOO: Will the committee please take their

proprietary documents with them. You should not leave anything behind.

[Whereupon, at 4:55 p.m., the meeting was recessed, to reconvene at 8:00 a.m., the following morning, Friday, July 31, 1998.]