DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

MEETING

Tuesday, June 10, 2003

8:30 a.m.

Holiday Inn Select
8120 Wisconsin Avenue
Bethesda, Maryland 20814

PARTICIPANTS

Glenn Braunstein, M.D., Chairman
Dornette Spell-LaSane, A.N.P, M.H.A., Executive Secretary

MEMBERS

Marie C. Gelato, M.D., Ph.D.
Deborah Grady, M.D., M.P.H.
William V. Tamborlane, M.D.
Dean Follman, Ph.D.
Paul Woolf, M.D.
Nelson Watts. M.D.
David S. Schade, M.D.

CONSUMER REPRESENTATIVE

Nancy Worcester, Ph.D.

NON-VOTING INDUSTRY REPRESENTATIVE

George Goldstein, M.D., F.A.A.P.

SPECIAL GOVERNMENT EMPLOYEE CONSULTANT (VOTING)

Jose Cara, M.D.

GUEST SPEAKER (NON-VOTING)

Harvey John Guyda, B.Sc. (Med), M.D., FRCPC

FDA REPRESENTATIVES

David Orloff, M.D.
Dragos Roman, M.D.
Robert Meyer, M.D.

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. BRAUNSTEIN: Good morning. I'd like to call the meeting to order. I'm Glenn Braunstein. This is the Endocrinolgic and Metabolic Drugs Advisory Committee Meeting.

We'll start by having introductions of the individuals around the table. We'll start with Dr. Meyer.

DR. MEYER: I'm Dr. Robert Meyer. I'm the Director of the Office of Drug Evaluation II in CEDR.

DR. ORLOFF: I'm David Orloff, Director of the Division of Metabolic and Endocrine Drug Products in CEDR.

DR. ROMAN: I'm Dragos Roman, Medical Officer, Division of Metabolic and Endocrine Drug Products.

DR. FOLLMAN: I'm Dean Follman, Assistant Institute Director for Biostatistics at NIAID.

MS. SPELL-LASANE: Dornette Spell-LeSane, Executive Secretary for the Committee.

DR. BRAUNSTEIN: I'm Glenn Braunstein, Chairman of Medicine, Cedars-Sinai Medical Center.

DR. CARA: I'm Jose Cara, Division Head of

Pediatric Endocrinology and Diabetes at Children's Hospital of Michigan, Wayne State University in Detroit.

DR. TAMBORLANE: I'm Bill Tamborlane. I'm Chief of Pediatric Endocrinology at Yale.

DR. SCHADE: I'm David Schade. I'm Chief of Endocrinology at the University of New Mexico School of Medicine.

DR. WOOLF: I'm Paul Woolf, Chairman of Medicine, Crozer Chester Medical Center.

DR. GELATO: Marie Gelato, Professor of Medicine, SUNY Stonybrook.

DR. WATTS: Nelson Watts, an endocrinologist at the University of Cincinnati.

DR. WORCESTER: Nancy Worcester, professor, University of Wisconsin Madison--the consumer rep on this panel.

DR. GOLDSTEIN: I'm George Goldstein, Vice President, Regulatory Affairs, Mankind Corporation--

DR. BRAUNSTEIN: Thank you.

DR. GOLDSTEIN: --industry representative.

DR. BRAUNSTEIN: Thank you.

Ms. Spell-LeSane will then read the conflict of interest statement.

Conflict of Interest Statement

MS. SPELL-LeSANE: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a 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 interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest with this meeting, with the following exception.

Dr. Glenn Braunstein has been granted a waiver, under 21 U.S.C. 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act, for ownership of stock in a competitor valued between $5,001 to $25,000. Because this stock interest falls below the de minimis exemption allowed under 5 C.F.R. 2640.202(a)(2), a waiver under 18 U.S.C. 208 is not required.

Dr. William Tamborlane has been granted a waiver under 18 U.S.C. 208(b)(3) for his membership

on an unrelated advisory board for a competing firm. He receives less than $10,000 a year.

Dr. Paul Woolf has been granted waivers under 18 U.S.C. 208(b)(3) and under 21 U.S.C. 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act for ownership of stock in a competing firm, valued between $25,001 and $50,000.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

With respect to FDA's invited guest speaker, there are reported interests which we believe should be made public to allow the participants to objectively evaluate his comments.

Dr. Harvey Guyda owns stock in Pfizer, and has attended scientific meetings sponsored by Serono, Pharmacia and Novo Nordisk in the past. He has also attended a scientific program sponsored by Genentech, at one time registered a few patients in their post-marketing surveillance program, and was a paid consultant on one occasion when he attended a meeting.

In addition, we would like to disclose

that Dr. George Goldstein is participating in this meeting as an acting industry representing, acting on behalf of regulated industry. 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 from such involvement, and 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 involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. BRAUNSTEIN: Thank you.

Dr. David Orloff will give the Welcome and Introductory Comments.

Welcome and Introductory Comments

DR. ORLOFF: Thank you.

I want to start by thanking in advance the members of the committee, consultants and guests, for their participation in this meeting.

FDA advisory committees serve critical functions in FDA's regulatory decision-making

process, and we very much appreciate the time and effort of all who have agreed to participate, with the full realization of the value of your time and the significance, therefore, of this sacrifice.

Let me also note that there are two members of today's committee for whom this meeting marks the end of their term on our official roster. They are Drs. Marie Gelato and Dr. William Tamborlane. |I would like to thank them formally for their valuable contributions over the past three years, and to say that I hope and expect that we will be calling on them as consultants and/or guests in future meetings.

Finally, I wish to welcome back Dr. Glenn Braunstein to the committee and to the chair position he has generously and skillfully filled in the past.

Now, to the subject of today's meeting. This meeting is taking place a little less than 16 years after an earlier FDA advisory committee was convened to discuss the methodological approaches to and endpoints of the safety and efficacy of growth hormone in pediatric patients with idiopathic short stature. The committee at that time readily agreed on the need for final heights

in the context of a blinded, randomized placebo-controlled trial in order to determine if, and to what degree, non-syndromic children--short but not meeting criteria for growth hormone deficiency would achieve final heights in excess of those predicted at baseline.

Leading up to that 1987 advisory committee meeting, the 1983 National Institutes of Child Health and Human Development Conference on uses and possible abuses of human growth hormone, looking toward the imminent approval of recombinant human growth hormone and resultant unlimited availability of the drug, concluded that there was "an urgent need for therapeutic trials to determine the effect of human growth hormone in short children who do not have growth hormone deficiency."

Indeed, over the 20 years since that time, there seems to have been general agreement in the field on the need for data on clinical safety and efficacy in what's called "non-growth hormone deficiency short stature" in order to inform final judgment on the wisdom of use of growth hormone in these children. More recently, in a 1997 Guidelines document on the use of recombinant growth hormone in children from the American

Academy of Pediatrics, the product of a panel of pediatricians, investigators, psychologists, psychiatrists and ethicists--among others--caution was advised, in light of the lack of data addressing this use of growth hormone.

The central question of today's meeting is, now that we have the data that will be presented, are they adequate to support the safety and efficacy and to guide the safe and effective use of human growth hormone in children with non-growth hormone deficient short stature.

We've asked Lilly to present the results of their pivotal study, as well as the supportive data that address the safety and efficacy to growth hormone for this new indication. In our discussions with the company leading up to the meeting, we requested that at a minimum they focus their presentation on several areas that we believe require discussion. They are as follows.

Obviously--what is the effect on linear growth of growth hormone administration in children with severe idiopathic short stature. What is the safety profile of growth hormone in these patients? Specifically, is it different than the safety profile in other pediatric populations?

Is there a need for growth-enhancing therapy in such children? Will the endorsement of the use of growth hormone in non-syndromic children not meeting criteria for GHD mean that growth hormone deficiency and idiopathic short stature will be lumped together into a category defined by diagnostic exclusion, such that growth hormone deficiency itself will no longer be formally diagnosed; or, worse yet, perhaps lead to overall less thorough evaluation of children with extreme short stature?

And, finally, to the extent that approval for the treatment of non-growth hormone deficient short stature may be construed as treatment of normal or of short normal children, what are the risks of off-label use to enhance the height of children who are simply shorter than they or their parents might want them to be?

Lilly has produced a briefing document that addresses these issues and questions, as well as others. They have presented the data from their pivotal placebo-controlled trial of growth hormone in non-GHD short stature, with final height as the primary efficacy parameter. They've also presented the results of a supportive, open-label dose

response study in somewhat younger children. And, finally, they have summarized the data from a published meta-analysis of trials of growth hormone in idiopathic short stature.

Note also that the sponsor has proposed and outlined a risk-management program to obviate inappropriate or injudicious use of growth hormone in children with short stature.

This advisory committee meeting will take a format that is a departure from what has been the usual in deliberations on pending drug applications by the Division of Metabolic and Endocrine Drug Products; that is, in the absence of disagreements over the facts of the case--in other words, the results of the analyses of the data from the trials--FDA will make no formal presentations. We've asked Lilly to present their data and to address the concerns raised in earlier discussions, as I've noted. The Division will do its utmost to respond to any questions from the Chair or from the Committee, as they may arise.

Finally, the Division has also asked Dr. Harvey Guyda of the Department of Pediatrics at McGill in Montreal, and an important researcher and voice in the growth hormone academic community, to

participate in the discussion, and to present his views on the matter before the Committee and the Agency.

The Division, in discussion with the company, has formulated a series of questions in order to frame the discussion after the presentations. Some of the questions will require specific expertise that not all of the committee possess--we realize that. And I'll review the questions in more detail when I make my formal charge to the committee.

And I turn it back to Dr. Braunstein.

DR. BRAUNSTEIN: Thank you, Dr. Orloff.

We'll now move into the presentation by Lilly. And I think that probably, as far as the format's concerned, we'll ask the committee to hold all questions until after the full presentation has been made. We invite you to write down the questions, and then we'll have plenty of time to ask them.

I believe Dr. Gregory Enas is going to make the initial presentation.

Sponsor Presentation

Introduction

DR. ENAS: Thank you, Chairman Braunstein--and good

morning. Thank you, Dr. Meyer and Dr. Orloff, members and guests of the Advisory Committee and the FDA. Thank you for this opportunity to present this data that Dr. Orloff has briefly overviewed for you in the treatment of pediatric patients who have non-growth hormone deficient short stature.

My name is Greg Enas, and I'm the Director of U.S. Regulatory Affairs for Endocrine Research and Development with Eli Lilly and Company. We have the opportunity today to provide information about this supplemental indication for this marketed product in children now with non-growth hormone deficient short stature.

Humatrope has previously been approved by the agency for children who are growth hormone deficient, as well as for girls with Turner's syndrome who have short stature without having growth hormone deficiency.

As you can see, the approved dose has been increased to 0.30 mg per kg per week, while in Turner's syndrome a weekly dose of 0.375 mg per kg per week has been approved. Greater efficacy has been observed with these higher doses.

Similarly, other recombinant human growth

hormones have been approved to treat short stature in various patient populations, with doses ranging from 0.16 to 0.70 mg per kg per week.

This morning, we will use the trade name Humatrope when we discuss the Lilly recombinant human growth hormone, and we will use and refer to either "somatropin" or "growth hormone" when we refer to all recombinant human growth hormone approved in the United States.

Note that none of the previous new drug applications leading to approval for somatropin in the U.S. have included randomized double-blind placebo controlled final height data, and this morning we have the opportunity to discuss such data with you.

Our clinical development program in children with non-growth hormone deficient short stature commenced following this plea from the National Institute of Child Health and Human Development International Conference on the Uses and Abuses of Growth Hormone. They stated that there was an urgent need for therapeutic trials to determine the effect of growth hormone in short children who were not growth hormone deficient. Four years later, guidance was received from the

Endocrinologic and Metabolic Drugs Advisory Committee asking that a study in this patient population, for which there is no approved treatment, should be a randomized placebo-controlled study, whereby patients should be treated and followed until their ultimate final height was achieved. And subsequent to that recommendation, Eli Lilly and Company and NICHD co-sponsored what we believe to be the first and only placebo-controlled study to final height, in this or any other growth disorder.

Though a number of patient populations with short stature are now indicated for treatment with growth hormone here in the U.S., we are aware that this potential new indication may raise a number of issues and questions. To ensure that these potential issues are addressed, the following questions will be answered in the presentations that follow.

First, how will potential risks be managed and safety be monitored?

Second, will this indication obviate the need for diagnostic evaluation in children with growth disorders?

Third, will this indication open the

floodgates for inappropriate use?

Fourth, are there ethical issues regarding growth hormone treatment of non-growth hormone deficient short stature?

And, fifth, is it appropriate to treat patients whose short stature is not clearly associated with a defined disease?

Sixth, should psychological or quality of life benefits be required outcomes of treatment with growth hormone?

And, finally, what is the clinical relevance of the efficacy?

To address these questions and provide a complete perspective on this new indication, we have invited a number of external consultants to participate in this meeting. In particular, Drs. Raymond Hintz and Margaret MacGillivray will make presentations from the podium. Drs. Judith Ross, Melvin Grumbach, Gary Koch and Ron Rosenfeld are also here with us and are available to address any questions the committee might have.

Our presentation will begin with Dr. Hintz, and he will provide the rationale for treatment in this patient population. Following Dr. Hintz, Drs. Cutler and Quigley will provide the

evidence for the efficacy and safety of this treatment, as well as an overview of the risk-management program being proposed, and an overall assessment of the benefit-risk profile.

Dr. Cutler is the Medical Director for the Humatrope product team at Eli Lilly, and Dr. Quigley is a Senior Clinical Research Physician in the Endocrine Division of Lilly U.S.A. Dr. Margaret MacGillivray, Professor of Pediatrics at the University of Buffalo will provide concluding statements. Following her remarks, Drs. Cutler and Quigley will be here at the podium to facilitate responses to any questions that you may have this morning.

With that, I now introduce Dr. Raymond Hintz, Professor of Pediatrics at Stanford University, who will discuss the rationale for Humatrope treatment. Dr. Hintz has nearly 30 years of clinical and research experience in the etiology, diagnosis and management of childhood growth disorders, and has authored over 200 publications in this area.

Dr. Hintz.

Rationale for Treatment

DR. HINTZ: Thank you. Greg. Good morning,

ladies and gentlemen. As Greg has told you, I'm here today to discuss the rationale for growth hormone treatment in patients with non-growth hormone deficient short stature.

First of all, some definitions, for those of you that are not pediatricians. "Growth failure" is a decline in the growth rate of linear growth. "Short stature" has been defined by both American Academy of Pediatrics and American Association of Clinical Endocrinologists, as well as the Growth Hormone Research Society and, for that matter, Lawson Wilkins Pediatric Endocrine Society, as height more than two standard deviations below the mean for age and sex.

There are many endocrine and non-endocrine causes of growth failure and short stature. And the Growth Hormone Research Society, in a recent statement, recommended investigation of children with short stature whose height falls below the minus-two standard deviation score.

Again, to orient you to what is short stature, this is a chart familiar to every pediatrician, and probably to every parent, in which on the y-axis is plotted the height, and on the x-axis is plotted age in years--in this case,

from 2 to 20 years of age. And there are lines indicated--the 0 percentile which is, of course, the mean, and plus or minus two standard deviation marks.

The plus-two standard deviation mark is the equivalent of 97.7th percentile, and the minus-two standard deviation is the equivalent of the 2.3 percentile. And this is the generally accepted definition of the normal range.

In terms of adult height, this means that a male of 5'3" or a female of 4'11" is at the minus-two standard deviation mark.

So why should one treat short stature? Children and adults with short stature, irrespective of cause, may well have disadvantages compared to their peers. On this slide is summarized some of the studies in the literature about the disadvantages of short stature during childhood and during adulthood.

Second, growth hormone treatment, in many cases, improves growth and effectively corrects short stature. Indicated here is a history, again, of the approved uses of growth hormone in this country, starting with the approval of rDNA growth hormone in 1985. Since that time, chronic renal

insufficiency, Turner's syndrome, Prader-Willi syndrome and small-for-gestational age infants who fail to catch up have all been approved, and it is important to note that all the pediatric indications approved after 1985 are for non-growth hormone deficient short stature conditions.

And we're here today to propose to you that non-growth hormone deficient short stature also be approved for growth hormone treatment.

So, just to emphasize: these patients are heterogeneous in their etiology, but on the other hand, so are growth hormone deficiency, Turner syndrome, and small-for-gestational-age infants. So the fact that they are heterogeneous in etiology is not unique to this group.

In addition to heterogeneous in etiology, they're heterogeneous in phenotype--but, again, so are growth hormone deficiency, Turner syndrome, and small-for-gestational-age infants.

On this slide, courtesy of Dr. Judy Ross, is a pair of fraternal twins. Julian, we'll call him, is essentially at the mean height for his age, and his brother James, who's almost a head shorter, is at the minus-2.8 standard deviation score. And this is typical of what we see in this syndrome--short

stature equivalent to growth hormone deficiency and the other causes of growth hormone failure--normal growth hormone tests; etiology is undefined in most cases; diagnosis has to be by excluding all the other important endocrine and non-endocrine diseases that can cause short stature. And, at the moment, these children are not eligible for growth hormone treatment.

So the features of this syndrome are that they have growth failure during childhood and their height is below the minus-two standard deviation score. There's actually no distinguishing phenotypic features in these patients, and amongst the heterogeneous etiologies that we can identify--familial and genetic abnormalities in the growth hormone IGF axis and abnormal growth plate response to growth hormone. And they do have a unimodal distribution of their height deficit.

Shown on this slide is a cartoon showing the normal short stature population shown here in white, in which the mean height at the time of reaching adult life is 5'9" for males in our society, and 5'4" in females. But, as is true of almost every biological variability, there's variation around the mean, so that this shows that.

The patients that we've defined as non-growth hormone deficient short stature have a peak height close to minus-three standard deviations. And, in terms of their adult heights, they are seven to eight inches shorter than their peers who are within the normal range.

So, let's review who is and is not eligible for growth hormone therapy under the present approval structure.

Eligible are patients that have a peak growth hormone below a certain threshold--frequently 7 or 10 on a series of testing, and these patients are classified as "growth hormone deficient" and eligible for treatment for growth hormone deficiency.

Four non-growth hormone disorders have been approved so far: Turner's syndrome, chronic renal insufficiency, Prader-Willi syndrome, and small-for-gestational-age children--irrespective of their growth hormone secretion status or, for that matter, degree of short stature.

Those that are ineligible at this time are those who have a peak growth hormone response above a certain threshold, who are now terms "non-growth hormone deficient," despite the fact that they are

equivalent short stature to those with growth hormone deficiency and other non-growth hormone deficient conditions.

So why should children with non-growth hormone deficient short stature be eligible for growth hormone? Well, first of all, as I've already told you, growth failure in these patients is equivalent to that in other growth disorders. Shown on this slide is a compilation of data from the literature. On the left axis is a their height standard deviation score. The pale blue outlines the patients that are in the normal range. Zero, again, is the 50th percentile.

And you can see that whether you have growth hormone deficiency, chronic renal insufficiency, Turner's syndrome, SGA, or non-growth hormone deficient short stature, all of these patients are close to the minus-three standard deviation score at the time that they are started on treatment. So they are indistinguishable.

Second, untreated patients do not achieve their adult height prediction, and this is shown in a variety of studies in the literature. And Dr. Cutler will later present data from the controlled

study of patients with non-growth hormone deficient short stature, showing that the control patients failed to reach their predicted adult height.

Growth hormone treatment in other conditions actually treats the short stature or growth failure, not the disease. Shown on this slide, on the left panel, is a patient with Turner's syndrome. On the right is a patient with non-growth hormone deficient short stature. And you can see that the patient--this happened to be Halloween time, so that's her goody back--the patient with Turner's syndrome has a height that's about two years behind--two to three years behind the height of her age-mates, so that she is at the minus-three standard deviation mark. And on the right there's a similar situation in the boy who's 11 years old.

So the degree of short stature is similar and, in fact, the response to treatment is similar and clinically meaningful, as we will show you.

We do not feel that an unknown or heterogeneous etiology of a condition should justify exclusion from treatment. Shown on this slide is a listing of some of the diseases that we--conditions of unknown or heterogeneous etiology

that certainly deserve and receive treatment. And if you scan down the list, I suspect that a majority of the audience has, or is now on treatment for some of these conditions; most commonly, perhaps, hypercholesteremia and hypertension.

And then, finally, non-growth hormone deficient short stature is responsive growth hormone treatment. This has been shown by a long history of research. Between 1964 and '71, early studies demonstrated an increase in growth rate in patients with non-growth hormone deficient short stature. And, as I look around the room, there are several people in the room that have published studies on this.

In 1983, as Greg has already told you, the NICHD International Conference recommended studies of growth hormone deficiency treatment in non-growth hormone deficient conditions. And then also, in 1987, the FDA advisory committee meeting recommended placebo-controlled studies to final height. And between 1985 and 2000, more that 40 studies were published on growth hormone treatment in non-growth hormone deficient short stature patients.

Shown on this slide is a study that I was a lead author on, sponsored by Genentech, published in the New England Journal in 1999. You can see that we had a total of 80 patients that reached adult height, and they were treated with .3 mg per kg per week of a recombinant growth hormone. At the beginning of treatment they were at nearly minus-three standard deviations for height on the average, and in the first year there was a placebo control in which they did--I'm sorry, not a placebo, but a non-treatment control group that, over that year of observation, did not have any significant increase in their stature.

On the other hand, the patients that were treated with growth hormone at that dosage, within two years the average was within the normal range and continued treatment brought them up so that at the end of the study they'd gained almost two standard deviations in their height.

So, what we're here today to do is discuss the studies that Lilly has done in the non-growth hormone deficient short stature patients between 1988 and 2001. But before I turn the podium over for that discussion, let me just review the key reasons why children with non-growth hormone

deficient short stature should be eligible for growth hormone treatment.

First of all, growth failure in these patients with non-growth hormone deficient short stature is equivalent to that in other growth disorders. Second, growth hormone treatment in other conditions treats the short stature or growth failure, not the disease, and it is, in fact, unfair to not offer such treatment to children that have just as much of a problem. And then, finally, unknown or heterogeneous etiology does not justify exclusion for treatment.

And I'd now like to have Dr. Gordon Cutler, from Eli Lilly, come and present the data on the efficacy.

Efficacy

DR. CUTLER: Thank you, Dr. Braunstein, members and guests of the Advisory Committee, Dr. Orloff.

During the efficacy portion of the presentation I will address four questions. First, is growth hormone treatment effective in children with non-GHD short stature? Second, is there a dose response for the dose of .37, compared to .24 mg per kg per week? Third, are there supportive

published data? And, fourth, is the efficacy similar to that in Turner's Syndrome and other approved indications?

Implicit in these questions is the goal of safe and effective treatment for children with non-GHD short stature who are just as short and just as deserving of treatment as children with other causes of growth failure. We seek your recommendation that Humatrope be approved for the treatment of these children based on the data that will be discussed today.

The data in our submission come from three sources: the pivotal study, GDCH; the dose-response study E001; and a meta-analysis published by Finkelstein and colleagues in 2002.

Let's begin with study GDCH. As recommended by the Endocrinologic and Metabolic Drugs Advisory Committee 16 years ago, the study GDCH was a double-blind, randomized, placebo-controlled trial to final height, with a planned enrolment of approximately 80 subjects, approximately 40 in each arm. The Humatrope dose chosen for the study was .22 mg per kg per week, given three times per week. When this study was designed, the approved dose was .18 for growth

hormone deficiency. Today, with GH doses up to .7 approved for pubertal patients with GH deficiency, .22 is considered a low dose.

In addition, daily or six times per week administration has been shown to be more effective than three times per week. And today growth hormone is usually given daily or six times per week.

Treatment in the study continued until height velocity fell below 1.5 centimeters per year, and the final height was then obtained one year later. Final height standard deviation score--or SDS-- was the primary endpoint of the study, because final height was the endpoint recommended by the Endocrinologic and Metabolic Drugs Advisory Committee for registration trials in non-GHD short stature 16 years ago.

The analysis populations for efficacy included all randomized population, the efficacy evaluable population, which had an on-study height measurement at or beyond six months of treatment; the final height population, which had a final height measurement, including eight patients who discontinued early and came back for a final height measurement after height velocity had fallen below

1.5 centimeters per year. And the final height population minus those eight patients--the protocol complete population--remained continuously on study until their final height measurement.

The primary analysis was an ANCOVA--or analysis of covariance--of the final height standard deviation score, with baseline predicted height standard deviation score as the co-variate. For all of the ANCOVAs that I will discuss today, baseline predicted height standard deviation score was chosen as the covariate because it is a strong predictor of final height.

In addition to the primary analysis, the protocol specified a number of sensitivity analyses which are listed here. Since all of these analyses are in the briefing document, this presentation will focus only on the most important results.

The baseline characteristics of patients, randomized to the two treatment arms, were similar, and there were no statistically significant differences between groups. The mean age was 12-1/2; the mean height standard deviation score was minus 2.8, which is similar to the height of untreated patients with GH deficiency, or Turner's syndrome.

The next slide will provide the primary analysis. The light blue shaded region represents the lower half of the normal height SDS range as defined by the American Academy of Pediatrics. Humatrope results are in green, placebo in pink. After treatment for a mean of 4.4 years, the mean final height standard deviation score of the Humatrope group was within the normal range, at minus 1.8, and was significantly greater than that of the placebo group, which remained below normal at minus 2.3. By ANCOVA, the mean treatment effect corresponded to 3.7 centimeters. Thus, the primary analysis indicated that Humatrope is effective in increasing the final height of children with non-GHD short stature. This is what we set out to learn 16 years ago.

We next asked: did the fact that some patients were not available for final height measurements bias the primary analysis? To answer this, we examined efficacy in the broader efficacy evaluable population because if the primary analysis had been biased by the drop-out of poorly responding patients the efficacy in this broader population would be lower.

This slide shows, in the left panel, the

protocol-specified ANCOVA of "last observed height standard deviation score." The mean treatment effect corresponded to 3.8 centimeters, nearly identical to that of the primary analysis. The right panel indicates a repeated measures analysis of height standard deviation score at age 18 years, which is a statistical approach complementary to the analysis of last observed height SDS. The mean treatment effect corresponded to 5.0 centimeters per year. Both of these analyses were highly statistically significant.

These modified intent-to-treat analyses, by their close similarity to the primary analysis, provides strong evidence against drop-out bias in the primary analysis. As a further test of such bias, we performed intent-to-treat analyses for all 71 randomized patients as assigned. By both parametric and non-parametric approaches, the Humatrope-treated patients had significantly last-observed height SDS, and the magnitude of the effect from the parametric analyses was similar to that of the primary analysis.

Thus, the close similarity of the estimates of treatment effect among the primary, modified intent-to-treat and intent-to-treat

analyses argues against drop-out bias in the primary analysis, and provides clear evidence that Humatrope is effective in increasing the final height of patients with non-GHD short stature.

I have not yet, however, addressed this question: given that intent-to-treat analyses are ordinarily preferred for clinical trials, why was the primary analysis restricted to the final height population? The answer relates to uncertainty about how the growth hormone treatment effect would evolve over time.

There was concern that growth hormone might accelerate not just height velocity, but also bone maturation. This would cause a transient increase in height relative to control that would not be sustained because of earlier cessation of growth in the treated patients. Thus, the maximum treatment effect might occur during treatment, and the inclusion of non-final height data from this period might lead to an overestimate of the treatment effect. So it was to avoid any possibility of overestimating the treatment effect that the primary analysis was restricted to patients with final height measurements.

Well, now that the results are available,

let's examine whether or not growth hormone accelerated bone maturation, and whether or not the pattern of the treatment effect was a transient increase and decline.

This slide shows bone age on the y-axis by year of study in the final-height population, the non-final-height sub-group of the efficacy evaluable population, and the full efficacy evaluable population. In each of the groups there were no significant differences between bone age in the placebo treated and the Humatrope-treated patients. Thus, for the growth hormone regimen used in this study, growth hormone did not accelerate bone maturation. Given this result, one would predict that the temporal pattern of the effect would not be an increase and then decline, and this is, in fact, what was observed, as shown on the next slide.

This slide shows the increase in height standard deviation score over baseline for the patients in each group. And, for this analysis, the time at which final height or the last observed height was measured was set equal to zero in order to synchronize the observation around final or last observed height. The temporal pattern of the

treatment effect was one of a gradual divergence of the two groups; a gradual increase over the initial years of the study, followed by stabilization, but not a decline in treatment effect, during the three years before final height measurement.

For example, in the final-height population, the mean treatment effect ranged from .42 to .51 standard deviation score over the three years prior to final height measurement. A similar treatment effect of 0.55, rounded to .6 on this slide, was also seen in the non-final-height sub group. Apparently, the mean treatment duration of three years in this group was sufficient to reach the maximum effect.

The combination of these two groups, which comprises the efficacy evaluable population also showed a quite stable treatment effect but not a decline over the three years prior to last observed height.

The evidence on this slide, against a transient increase in the decline of the treatment effect removes the principal objection to the inclusion of non-final-height data in the efficacy analysis. Based on these data, for this regimen, the concern that such data would lead to an

overestimate of the treatment effect is not justified.

One additional point about this slide: the fact that the treatment effect stabilizes and sort of remains stable during continued treatment does not mean that it would remain stable if treatment were discontinued early. Early discontinuation has been shown in a number of studies to result in a rapid deceleration of height velocity, and for this reason growth hormone for all of the pediatric indications is normally continued until near adult height.

The next slide simply shows mean height standard deviation score by year on study for the two treatment groups. And as in the study that Dr. Hintz showed, by about two years into treatment, the mean height SDS was at the lower limit of normal, which means that approximately half of these children had caught up to their peers and now had height SDS's within the normal range for age and gender.

Let's now summarize the key results from this study. The primary analysis indicated a treatment effect corresponding to 3.7 centimeters; the modified intent-to-treat corresponding to 3.8

to 5 centimeters; and the full intent-to-treat analyses confirmed was significantly greater height standard deviation score of the Humatrope-treated patients.

Now, given the 3.7 centimeters efficacy from this study--height increase--we wondered did the low dose of .22, and the low-dose frequency of three days per week result in a smaller height increase than would have been observed with a larger growth hormone dose given more frequently.

Results from the E001 dose-response study will address this question. Study E001 was a three-arm randomized, dose-response study comparing a lower dose--.24--with a higher dose--.37. There was also an intermediate dose with a lower dose for one year and the higher dose thereafter. The primary analysis was a comparison between the lower and the higher dose of the increase in height velocity over the first two years. There was then an extension to final height to examine the dose effect on final and last-observed height.

Study E001 was a European multi-center study conducted in 10 countries, and final height was defined as the last height measurement after height velocity fell below 2 centimeters per year.

Since results of all three treatment arms are in the briefing document, in this presentation I will focus just on the comparison of the lower and the higher dose arms.

The analysis populations for this study were the all-randomized population; the two-year height velocity population who completed two years of treatment; and the final-height population that had a final-height measurement. And because I will be focusing just on two arms, the relevant numbers of patients in the higher and lower-dose arms are shown in the brackets, with the middle dose omitted.

The primary analysis--on the next slide--was an increase in height velocity measured from zero to two years between the higher and lower-dose arm. Secondary analyses included an ANCOVA of height-last-observed height SDS, and a repeated measures analysis of height SDS at age 18 years, as in the previous study.

We also examined final height minus baseline predicted height as a measure of the overall efficacy within each dose group. And for this analysis the final height of each patient is compared with the height that they were predicted

to achieve without treatment.

The baseline characteristics of patients randomized to the higher and lower-dose arms were similar, although the patients randomized to the higher dose were slightly taller at baseline. Mean age was 9 to 10, or about two years younger than in the previous study.

The next slide shows the primary analysis. After two years of treatment, mean height velocity for the lower-dose arm had increased to 7.5 centimeters per year; for the higher-dose arm, to 8.5 centimeters per year. The between-dose effect--or the incremental increase of the higher compared to the lower-dose was .8 centimeters per year, which was highly statistically significant. Thus the primary analysis indicated that the .37 dose is more effective than the .24 dose in the increase in two-year height velocity.

What we next asked: what was the effect of the higher dose of last-observed height SDS, and height SDS at 18 years? This slide shows, in the left panel, the ANCOVA of last-observed height SDS. The between-dose effect corresponded to 3.3 centimeters. The right panel indicates the repeated measures analysis of height SDS at age 18

years. The between-dose effect corresponded to 2.8 centimeters. Both of these effects were statistically significant.

Now, these between-dose effects refer to the incremental effect--the incremental height gain--of the higher-dose group compared to the lower-dose group, and should not be confused with the overall efficacy of the higher-dose group, which I will discuss in a moment. Now, just as in the previous study we showed that growth hormone did not accelerate bone maturation, it was important in this study to examine whether or not the higher .37 dose accelerated bone maturation relative to the lower dose.

This next slide shows bone age by year on study for the final-height population, the non-final-height sub-group of the patients who complete two years of treatment, and the full two-year height velocity population. In all three groups there were no significant differences in the rate of bone age progression between the two dose arms. And this is really reflected by the slope of the lines, because there is some slight imbalance in the baseline values. Thus, there were no dose-related differences in bone age progressions, and

the dose of .37 does not accelerate bone age relative to the lower dose.

Well, this concludes my comments on dose effect, and I'm now going to turn to the analysis of final height minus baseline predicted height as a measure of the overall efficacy within each dose arm. And, again, for this analysis we're comparing, within group, the final height of each patient with the height they were predicted to achieve without treatment.

On this slide, after a mean treatment duration of six-and-a-half years, the final height of the lower-dose group exceeded their baseline prediction by 5.4 centimeters, and for the higher-dose group, by 7.2 centimeters. Both of these results were highly statistically significant. Thus, by this measure of efficacy, the overall efficacy of the higher-dose group is 7.2 centimeters.

Now, the validity of this measure depends on the accuracy of the heights that the patients were predicted to achieve. So how accurate are these baseline height predictions? To examine this, we both reviewed the literature and the results of our own placebo-treated patients from

the previous study. And in the literature we found that, on average, when patients with non-GHD short stature are followed to final height without treatment, on average they fall slightly below their baseline predicted height. Similarly, in our own placebo-treated patients--on this next slide--in the left panel--bar--shown in pink, the mean final height of the placebo patients fell slightly below by .7 centimeters below their baseline prediction.

Now, this evidence that on average untreated patients fall slightly below their prediction led us to conclude that the amount by which a treated patient exceeds their prediction is a valid and, indeed, a conservative measure of overall efficacy. Thus, we concluded that the overall efficacy of the .47 dose is at least 7.2 centimeters.

Let's summarize, then, the between-dose effects and these overall efficacy results for this study.

The primary analysis indicated a greater increase in two-year height velocity by .8 centimeters per year, and a greater--in the secondary analyses--a greater overall height gain

in the higher dose, corresponding to 2.8 to 3.3 centimeters. And the overall efficacy for the lower dose was 5.4 centimeters; for the higher dose, 7.2 centimeters.

The next two slides will summarize the final height SDS results for both of these studies. This summary provides an alternate way of looking, or viewing, the overall efficacy of the .37 dose relative to this within-group comparison I just gave you earlier, of the final height compared to what they were predicted.

This alternate way of viewing the data is that it has two components: it's the incremental effect of the higher relative to the lower dose, which was 2.9 centimeters from the final-height SDS ANCOVA, which is shown here, plus whatever the overall efficacy of the lower dose is. Now, I gave you earlier a within-group approach to that, but this can also be estimated from the pivotal study, which used a slightly lower dose. That study gave an efficacy for the .22 dose at 3.7 centimeters, and combining these two components, one gets an overall efficacy of 6 to 7 centimeters, or about one SDS. This estimate is similarly to the 7.2 centimeters estimate that I gave you for the

within-group comparison against baseline predicted height, and it simply shows the internal consistency between that within-group analysis and these between-group analyses on this slide.

Now, the individual final-height data that's represented by each of these bars will be shown on the next slide. For the placebo-treated patients, shown in pink, most of the patients--most of their final heights fell below the normal range, and none of them exceeded the fifth percentile of the general population. By contrast, for patients treated in the higher-dose arm, 94 percent had final-height standard deviation scores that were within the normal range. And even the one patient who failed to reach the normal range had a height SDS gain of 0.9 from a very low starting point.

Now, the next slide will show these same final-heights plotted in relation to their individual baseline predicted heights; the heights they were predicted to achieve without treatment. These baseline predicted heights are shown in inches on the x-axis; the final-heights they achieved on the y-axis. A line of identity is this diagonal. And so the amount by which a patient exceeds this line is the amount by which they

exceed the height that they were predicted to achieve without treatment. So, for example, this patient ended up 6.4 inches above the height that he was predicted to achieve without treatment.

Now, if we examine the placebo-treated patients, we can see that most of them fell either on, near or slightly below--somewhat below--what they were predicted to achieve without treatment. By contrast, most of the treated patients exceeded what they were predicted to achieve, and particularly in the high-dose group--shown by these blue symbols--62 percent of these patients were more than two inches about their predicted height, and 31 percent were more than four inches above the height that they were predicted to achieve without treatment.

Well, given the efficacy observed in these studies, we asked: are there supportive studies in the literature on effectiveness of growth hormone in children with non-GHD short stature? To answer this we examined the recent meta-analysis by Finkelstein and colleagues, published last year. Since these results are in the briefing document, for the sake of time in this presentation I will only summarize their conclusion.

Based on four controlled studies to final-height, the authors concluded that the mean growth hormone effect on adult height in this group was 4 to 6 centimeters. A similar treatment effect was also seen in eight uncontrolled studies to final-height. Thus, published studies do support the efficacy of growth hormone in non-GHD short stature, and the magnitude of the effect in these other previous studies is similar to that observed in the Lilly studies.

We next asked: is the efficacy in non-GHD short stature similar to that in Turner's syndrome, which is an approved and widely accepted indication? And we chose Turner's syndrome for this comparison because it's the only previously approved indication for which controlled final-height data was required for the approval, and thus we can make an apples-and-apples comparison of the results. And we chose for the comparison the study that was most similar in design to that of our pivotal study, GDCH.

This next slide indicates that study GDCT was a randomized study with an untreated control group. This was performed in Canada, followed all the way to adult height. The growth hormone

regimen was .3--a dose of .3 given six times per week. And from the planned interim analysis, which was used to support the use of Humatrope for Turner's syndrome in 1997, the treatment effect from the primary analysis was 3.9 centimeters, quite similar to the 3.7 centimeters from the pivotal study; and from a sensitivity analysis, 5.4 centimeters.

In addition to this efficacy being similar to that in Turner's syndrome, the efficacy in non-GHD short stature is also similar to that in other indications, such as growth hormone deficiency. For example, in our registration trial--although the approval was based on short-term data--30 patients from our original registration trial for GH deficiency were followed all the way to adult height. The mean height SDS gain for those patients of 1.5 was very similar to the gain of 1.55 which was seen for the lower-dose arm of our E001 dose-response study, and was actually slightly below what we had seen in the higher-dose arm, which was 1.85. Thus, the efficacy in children with non-GHD short stature is similar to that in Turner's syndrome, and in other indications.

We then asked: how does the variability of

the height SDS gain in Turner's syndrome compare to the variability of that in non-GHD short stature? This was of interest, because some had predicted that non-GHD short stature, lacking a defined etiology, might have a more variable response to growth hormone.

The next slide shows these distributions of height SDS gain, with the percentage of patients with each range of gain on the y-axis, and the actual ranges of height SDS gain on the x-axis. So, for example, the patients represented by this bar gained 0 ti 1 SD, 1 to 2 SD, 2 to 3 SD, 3 to 4, 4 to 5, and so on. Patients with Turner's syndrome are shown in the lower panel. Patients with non-GHD short stature from the pivotal study in the middle panel, and from the dose response study, in the upper panel.

In each of these panels the distribution of height SDS gain is uni-modal and with similar variance. Thus, the variability in height SDS gain in children with non-GHD short stature is also similar to the variability that is seen in Turner's syndrome--and, for that matter, although we didn't plot it, a very similar variability is seen in GH deficiency.

In conclusion, consistent efficacy was demonstrated in the pivotal study, the dose-response study, and in the literature meta-analysis. The effect size was 3.7 centimeters for the low .22 dose; 7.2 centimeters for the higher .37 dose. The effect is therefore dose responsive, with greater height velocity increase, and greater overall height gain, with the higher compared to the lower dose. And the overall efficacy is similar to that seen in Turner's syndrome and other approved indications, such as growth hormone deficiency.

Well, given these mean height gains--3.7 centimeters at the lower dose, 7.2 at the higher dose--the question has been raised: what is the clinical relevance of these height gains?

This is not an easy question, because ultimately clinical relevance is unique to each patient. For one patient it may be a life-long dream of becoming a pilot, or pursuing any of the careers which encompass millions of jobs in the United States for which there is a minimum height requirement. For another child, it may simply be the desire to catch up to one's peers, to reduce the likelihood of being repeatedly mistaken for a

child three or four or five years younger; or being teased, bullied or excluded, simply because of one's side.

So let me conclude by summarizing the evidence that the height increases observed in these studies are sufficiently large to be clinically relevant.

First, most of the patients caught up with their peers and reached the normal height range during childhood. Second, there was a similar height benefit to that seen in Turner's syndrome and, indeed, in the other indications including growth hormone deficiency. Third, 62 percent of final-height patients in the higher-dose group gained more than two inches; 31 percent gained more than four inches; one gained more than six inches above their baseline predicted height that was expected without treatment. And 94 percent of final heights in the higher-dose group were within the normal range, thus conferring on these patients the lifelong benefit of normal adult statute.

This concludes the efficacy presentation, and Dr. Charmian Quigley will now present the safety data, the risk management program, and the risk-benefit discussion for growth hormone

treatment of these patients.

Dr. Quigley?

Safety

DR. QUIGLEY: Good morning, Chairman Braunstein, members of the committee, members of the FDA and guests.

Having heard the efficacy presented by Dr. Cutler, to allow you to adequately assess the appropriateness of an approval of treatment for this patient population, it's now my responsibility to present to you the safety.

And to do this, I'll take the same approach that Dr. Cutler took, and ask three questions. First, is somatropin safe in pediatric patients? Second, are there any new significant adverse events or safety concerns in this patient population? And, third, is there an increased frequency of the adverse events currently described in the product label in this population?

I should remind the audience that somatropin is not a new product. It has a 16 year safety history, and it can be estimate pharmacovigilance and post-marketing research studies that over 200,000 patients have been exposed to this product worldwide, across all

brands of the product, amount to something over half a million patient years of exposure--a truly sizable data base.

In this time, a well accepted safety profile has been developed in five currently approved pediatric indications at doses up to 0.7 mg per kg per week. A small number of uncommon but well characterized events have been found to be associated with growth hormone exposure, but these are considered relatively mild and typically transient.

Because of their importance, there are two key areas of focus with respect to growth hormone treatment, and these are the potential impact of growth hormone on carbohydrate metabolism and potential relationship to development of neoplasia.

Over this period of time, a comprehensive literature has been developed that addresses the safety in over 200 publications in the peer-reviewed literature. And, most recently, the Growth Hormone Research Society reviewed this literature and summarized, in a consensus statement, as follows.

They indicated that recombinant growth hormone has undergone and unprecedented level of

scrutiny that has lasted more than 15 years and continues today; concluding, "The extensive data to date collected on large numbers of children and adults treated with growth hormone indicates that for the current approved indications growth hormone is safe."

In discussions and correspondence prior to this meeting it was agreed that an appropriate approach to evaluating the safety in this new population would be to compare this population with the populations of patients for which Humatrope is currently approved: those with Turner's syndrome and growth hormone deficiency. So, on this slide I show the five studies--registration studies--that will be included in this safety comparison.

In the growth hormone deficient population--abbreviated as "GHD"--we have 333 patients who received doses ranging from .18 from .24 mg per kg per week in the registration study. In the Turner's syndrome population--abbreviated as TS--approximately 300 patients across the two different registration studies received doses ranging from .7 to .36 mg per kg per week. The number here in parentheses represents the total patient population, including those in the

untreated control group.

In the non-growth hormone deficiency short stature--abbreviated as "NGHDS"--again, close to 300 patients across the two studies received doses ranging from .22 to .37 mg per kg per week.

There are three key take-home points from this slide with respect to the similarities in this safety comparison. And that is the numbers of patients exposed; the doses of growth hormone that they received; and the patient years of exposure, which amount to over 1,200 in each patient group. There is one caveat, however, with respect to this comparison, and that is that study designs differed, patient populations differed, and so these comparisons must be judged with those points in mind.

The analyses that will be presented here in this safety section are listed on this slide--and I'll go through these one by one.

Beginning with patient deaths, fortunately there were few patient deaths in any of the studies. There was one patient death during study in a patient in the growth hormone deficient studies, and two patients died after study. The details are provided in your briefing document, so

I won't go into these. One patient in the Turner's syndrome study died during study, however this was a control patient not receiving Humatrope. And one patient in the non-GHD short stature study died after study, and I'll detail his findings shortly.

Similarly, rates of discontinuation due to adverse events were also low, amounting to no greater than 3 percent across any of the studies in any of the patient populations. I should point out that in this slide and the next slide, the column headed "n" represents only those patients receiving Humatrope, not the control patients.

Serious adverse events were generally slightly lower for patients in the non-growth hormone deficient short stature group than the other two patient populations, likely relating to the greater level of baseline abnormalities and disease in the other two populations.

Turning specifically to the serious adverse event of neoplasia, there were six cases of neoplasia during the growth hormone deficiency studies; one patient who underwent a new diagnosis of a craniopharyngioma; one patient who had the diagnosis of papillary thyroid carcinoma--this patient has previously received treatment for

leukemia, and this is a predisposing factor; and four patients who had recurrence or progression of preexisting intra-cranial tumors.

No patient in the Turner's syndrom studies suffered a neoplastic disease, and two patients in the non-growth hormone deficient short stature studies had neoplastic conditions--which I'll detail in the next two slides.

The first is a patient in study GDCH, our placebo-control trial, who was diagnosed at the age of 11 years with stage III-B Hodgkin's disease--a quite advanced stage of Hodgkin's disease--after only nine weeks on study. Now, in retrospective review of this patient's case, we discovered a number of factors that led to our conclusion that this patient very likely--and almost certainly--had this disease at study entry. The first was the fact that on a chest x-ray performed two months prior to study, the patient was reported to have a widened mediastinum. At the time the radiologist suggested that this might be due to a thymus remnant, but, in fact, it's well known that Hodgkin's disease commonly presents with mediastinal widening. Second, at study entry the patient had a high normal sedimentation rate of 32

mm per hour--you can see the reference range in parentheses--and had an elevated LDH--lactic dehydrogenase. This is a non specific marker of systemic disease.

By 12 weeks on study, the patient had a frankly elevated sed rate of 58, and continued to have an elevated LDH. And I reviewed this case with an external pediatric endocrinologist who concluded that the clinical features, and the fact that the patient had such advanced stage of disease at study entry, indicated that he did have sub-clinical disease at study entry--I'm sorry--the advanced stage of disease at diagnosis.

Now, moving to the second case, this is an unusual tumor called a "desmoplastic small round cell tumor." This was diagnosed in a 12-year-old boy in the lower-dose group of study E001, after six-and-a-half years on study. The patient discontinued from study at diagnosis and, unfortunately, died approximately four years later. We were subsequently able to find the karyotype report from this tumor, which showed that there was an unusual translocation, with the translocation break-points occurring at chromosome 11-P-1-3, which is the locus of the Ewing sarcoma gene, and

chromosome 22-Q-1-2, which is the locus of the Wilms tumor suppressor gene. It's very important to note that this karyotype is the hallmark of this tumor. And this translocation produces an oncogenic fusion gene whereby the five-prime portion of the Ewing sarcoma gene is placed upstream of the three-prime portion of the Wilms tumor suppressor gene. This is very important with respect to t the pathobiology of this tumor, because it's important to recognize the translocations are not associated with growth hormone therapy.

Furthermore, there has been no additional case of this tumor in a growth hormone treated patient, either in Lilly's pharmacovigilance database, or in the literature. I also reviewed this case with an external expert in the biology of the desmoplastic small round tumor--in fact, the individual who first reported the existence of these tumors--and he also believed that this was unrelated to the patient's growth hormone exposure.

Returning now to treatment emergent adverse events--or TEAEs--as expected in pediatric studies, the majority of patients did experience TEAEs, but most of these--also as expected--were

common childhood illnesses like pharyngitis, flu--typical things. There was some slight difference in the pattern of TEAEs that were reported across the different patient populations--again very likely relating to the different baseline diseases.

Importantly, there were no significant differences in the rates of TEAEs for the Humatrope versus the placebo group in study GDCH, or for the lower versus the higher-dose group in study E001; and no new adverse events were seen in the non-growth hormone deficient short stature population.

Now, with specific reference to the events that are currently listed in the Humatrope label, this table shows in the left column the events that are currently listed as events to be searched for in the Humatrope label, and the comparison is between the growth hormone deficient, Turner's syndrome, and non-growth hormone deficient short stature population. And the key from this slide is that for the non-GHD short stature population, rates of these common TEAEs are either lower--such as here, with otitis media--or similar to, such as disturbances of carbohydrate metabolism, the other two indications--indicating no increase in the rates of these well-known adverse events.

To evaluate the potential differences between doses with respect to adverse events, we have study E001 where, in the lower-dose group we see that serious adverse events were reported in 14 percent of patients, and in a similar rate of 19 percent of patients in the higher-dose group, with the intermediate dose group--which, in fact, received this higher dose of growth hormone for about three quarters of their time on study--having a much lower rate. So this obviously suggests no dose-related pattern in serious adverse event development.

Similarly, in treatment-emergent adverse events, we evaluated those events that occurred in more than a single patient during the course of the study. Nine events occurred most frequently in the lower-dose group; similar number of 11 events occurred most frequently in the higher-dose group; and 18 events occurred most frequently in the dose group that changed whilst on study. So there is no clear pattern of effect of different Humatrope doses on adverse event profiles.

Turning form our own studies to the literature, as I mentioned in the beginning there's really a comprehensive literature on safety in this

patient population--or in all populations--starting with the Kabi International Growth Study, the recent publication from Dr. Wilton in 1999 on the safety data from that study, addresses close to 26,000 patients, and over 62,000 patient years of exposure. The events here are reported as adverse events per 1000 treatment years. And what can be seen, comparing these different forms of growth failure and growth disorder that received growth hormone treatment is that idiopathic short stature--or what we would term "non-growth hormone deficient short stature," in fact has the lowest overall rate of adverse events across all of these different conditions.

Looking at some specific adverse events, a number of these are listed here in this first column that were evaluated in this report. Here I would like to point out that patients exposed to close to 35,000--that's a pretty decent number to be evaluating--and, again, what we saw here, as we did in our own studies, is that event rates are either similar to--such as arthralgia, the other conditions listed here--or lower than--such as Type II diabetes--than the other conditions receiving growth hormone treatment.

Similar data can be evaluated from the National Cooperative Growth Study, the U.S. study in which there have been over 100,000 years of patient exposure. The data here are shown in a slightly different way, in that event rates are shown relative to the percentage of the total database that the individual indication represents. So, for idiopathic short stature, there are over 5.5 thousand patients in the database at the time of this 2000 report, and 17 percent of the database is represented by this diagnosis. And you can see that for each of the conditions listed, all serious adverse events--sorry, "all adverse events," "serious adverse events," and then the individual events--the event rate occurrence for idiopathic short stature is less than the 17 percent of the database that these patients represent.

I'm turning now from adverse events to laboratory analyses, and here we'll focus on parameters that evaluate carbohydrate metabolism in both study GDCH and study E001, and parameters that evaluate insulin like growth factor 1.

First I'll orient you to the format of this slide, as subsequent slides show the same format. On the left axis is the reference--the

units of measures for the analyte of interest, given in typical U.S. units, and on the right y-axis, in Systeme Internationale units. The reference range is shown in the shaded blue area; placebo patients in pink on the left; Humatrope patients in green on the right.

Within each group, baseline values are shown in the left group of symbols, and last on-study values shown in the right group of symbols, and individual patients are shown by the open symbols, and solid symbols represent the means.

So, here it's obvious that there is no Humatrope effect on fasting glucose. We see essentially no change in the fasting glucose from baseline to endpoint, and no difference between placebo and Humatrope.

Similarly, in study E001, we see no dose effect on fasting glucose. Here we see the baseline points for the lower-dose group and the higher-dose group being very similar.

Turning to fasting insulins, the effect here is a slight increase in fasting insulin from baseline to endpoint. To evaluate this with more rigor, we then performed quantitative insulin sensitivity check index analysis, which integrates

both glucose and insulin to give a measure of insulin sensitivity--shown on this slide. And in this analysis, higher values represent higher insulin sensitivity. Lower values represent lower sensitivity.

What this analysis demonstrates is that there is significant variability across the patients in each of the groups--perhaps slightly more variability in the Humatrope group than the placebo group--but that there is no clear pattern of effect in either group, with some patients increasing, some patients decreasing, and some patients just staying the same. And so there is no obvious effect of Humatrope with respect to insulin sensitivity in this study.

Concluding the laboratory analyses with IGF-1, this graph represents IGF-1 as a standard deviation score. And we can see--we would have expected to see some increase in serum IGF-1 from baseline whilst on treatment, and the IGF-1 values stay well within the normal range throughout the duration of the study, and the peak achieved was, in fact, around 0 standard deviation scores.

So, to summarize the safety, this treatment in this patient population, we had a

single post-study death due to an unusual abdominal tumor, which is believed to be unrelated to Humatrope exposure. We saw no difference from growth hormone deficiency or Turner's syndrome for the rates of serious adverse events, discontinuations due to adverse events, or treatment-emergent adverse events.

There were no significant difference in adverse event rates between the Humatrope and the placebo groups in study GDCH, and between the lower and higher growth hormone dose groups in study E001.

Laboratory analyses showed no Humatrope effect and no dose effect on fasting glucose or hemoglobin A1c--I did not show you those data, but they are in your briefing document--and no significant Humatrope effect on insulin sensitivity. And, finally, the IGF-1 values remained within the normal range.

So, to conclude, these data demonstrate that somatropin is safe in pediatric patients. It has a well-characterized safety profile, with over 15 years of accumulated experience. There were no new significant adverse events or safety concerns in this patient population, and no increase in

frequency of the adverse events currently described in the product label.

So, in concluding, I have answered the three questions that I began this presentation with, to conclude that the safety profile of Humatrope in this patient population is similar to that in the currently approved indications.

Benefit-Risk Assessment and Risk Management Plan

DR. QUIGLEY: Well, I've demonstrated that Humatrope has an excellent safety profile. But to address the potential use of this product in a new population, Lilly is also proposing a comprehensive risk-management program.

And to evaluate this, I'm going to return to the questions that Dr. Enas asked at the beginning of this presentation. And in this section, I will address the first three questions that Dr. Enas posed, beginning with "How will the potential risks be managed and safety be monitored?"

Well, the cornerstones of a risk-management program are appropriate labeling and pharmacovigilance. But Lilly recognizes that there have been concerns raised about the potential for inappropriate use in this patient population. And

so we've gone beyond the standard risk-management to include a number of elements that create a comprehensive risk-management program that I'll detail in subsequent slides.

First, the proposed label wording, and that is: "Humatrope is indicated for the long-term treatment of non-growth hormone deficient short stature, defined by height standard deviation score less than or equal to minus-2.25, in pediatric patients whose epiphyses are not closed, and in whom diagnostic evaluation excludes causes of short stature that should be treated by other means."

Now, this restrictive label is highlighted here in yellow--the two key restrictive elements of the label. And this, in particular--the height standard deviation score of minus-2.25 recommended for this proposed label may lead you to ask: why did we choose this restriction?

The first reason was that we received recommendation from the FDA that for this patient population we should provide, within the label, guidelines to prevent over prescribing, which is a concern that has been raised. And thus we chose a guideline--a threshold that we feel will accomplish this goal.

This threshold reflects the pivotal trial inclusion criterion for height, as the majority of the patients in the pivotal trial were enrolled in the study under this height criterion. And, finally, this criterion will limit access by excluding all patients whose heights fall within the normal range--that is, above minus-2 SD scores, and excludes almost half of patients whose heights, in fact, do represent short stature by falling below minus-2 SD scores. And, in doing this, Lilly believes that we strike a balance between providing treatment to those for whom treatment is appropriate, and restricting access to this therapy from those who should not receive it.

With these restrictions in place, we maintain that no additional label restrictions should be required. Note that this is the only growth hormone label that contains any form of height restriction or threshold, and that this restriction excludes 46 percent of the patients who could be diagnosed as having non-growth hormone deficient short stature.

Now, a number of other factors have been suggested as possible factors to be included--or may be suggested as possible factors to include as

label restrictions, such as height velocity, or bone age, or target height. However, these are really not appropriate for inclusion as restrictions; this is the practice of clinical pediatric endocrinology. These are the factors that pediatric endocrinologists integrate when they're evaluating patients to make appropriate treatment decisions. So these should not be included as label restrictions, but should be left for the practice of clinical pediatric endocrinology.

Moving to the second element of our risk-management program, this focuses on sufficient education, which will ensure that physicians understand these label restrictions that I've just detailed, and understand the process for making an accurate diagnosis of non-growth hormone deficient short stature; and also that they are well aware of the benefit to risk profile that I will detail shortly. The methods utilized will by physician-to-physician educational programs and continuing medical education.

The third element of our risk-management program is limited marketing. WE have a small sales force of under 100 sales representatives, who will

undergo comprehensive training regarding the patient characteristics that represent this patient population , the diagnostic process that must be undertaken to make this diagnosis, and the benefit-risk profile. These sales specialists will call only on pediatric endocrinologists for this indication, and there will be no direct consumer advertising.

The fourth key element of our risk-management program is controlled distribution. And here I must point out that this has been in place ever since Humatrope was first launched in the mid-1980s, because of the concerns regarding potentially inappropriate prescribing. The first element of this is that a statement of medical necessity is required, both by Lilly and by insurers for all new patient diagnoses. And this collects information such as the diagnostic information, growth hormone test results, growth parameters, etcetera.

Second, Lilly--Humatrope is shipped only through Lilly-approved closed specialty pharmacies. It is not shipped to retail pharmacies. So a patient cannot simply turn up at the GP's office, get a prescription for Humatrope and go to the

corner drug store and get it filled. This simply cannot happen.

Third, Lilly monitors prescribing behavior. And if potential problems are detected on this monitoring, these are investigated and corrective action has occurred in cases where inappropriate prescribing has been detected, and can include denial of access to prescribing Humatrope. Further details of this process have been provided to the FDA.

Finally, how will we monitor safety in this risk-management program? There are two key elements here: standard pharmacovigilance, which is the collection of adverse event data, and the observational post-marketing research program. Within our pharmacovigilance system, which is a worldwide pharmacovigilance system, we screen for adverse events that may be associated with growth hormone treatment; we regularly evaluate any events that we detect for potential safety concerns; and we communicate any findings with worldwide regulatory agencies.

Now, our observational post-marketing research program is known as GeNeSIS--the Genetics and Neuro-endocrinology of Short Stature--and I'll

describe this a little further shortly. Returning to the specifics of the safety monitoring, these listed here are the precautions that are currently present in the Humatrope label to be evaluated. So the label states that "careful monitoring or follow-up is recommended for those with pre-existing scoliosis, skin lesions or tumors, hypothyroidism, insulin resistence and decreased glucose tolerance, intracranial hypertension, otitis media and other ear disorders, and slipped capital femoral epiphysis. And these conditions will continue to be monitored throughout post-marketing research, such that no further precautions are required for the Humatrope label.

Turning now to this post-marketing research program, as I mentioned, its name is GeNeSIS. It is currently running in 30 countries worldwide, at over 400 study sites, currently of which 140 are in the United States, and we are continuing to enroll addition sites on a progressive basis. Any Humatrope-treated patient at any study site is eligible to enroll, irrespective of whether they are currently receiving treatment or just starting treatment. And, in addition, there are two sub-studies within

this program that enroll untreated patients, to allow us to better characterize the relationships between Humatrope treatment and any efficacy and safety issues. And I'll provide a little more information on these subsequent.

Now, this slide provides some of the details. I won't go into the details of what the information is that we collect in the program, other than to highlight the fact that we collect a lot of information on history, diagnostic and efficacy information. But because I'm focusing on safety, I'm going to highlight what we collect with respect to the safety data.

In addition to the spontaneous adverse event data, this program is actually unique because we have, within the program, a module that solicits proactively a number of conditions that have been associated with growth hormone exposure. And so patients are asked about these on every study visit, and these are reported into the program at each visit.

Another key difference between this program and previous programs is that we have within it a sub-study that targets neoplastic disease, knowing that this has been a concern in

the community for a long time. The sub-study collects information on patients with a prior history of neoplasia who are either treated or not treated with growth hormone for long term. And then the other key difference in this program is that we also provide, as a safety tool, IGF-1 and IGFBP-3 as a service to all patients in the program.

The data are reported regularly, annually, to the study investigators in annual investigator meeting, and safety data as a whole are reported annually to regulatory agencies, and we also provide ad hoc reports whenever these are requested. In addition, the Lawson Wilkins Pediatric Endocrine Society requests and receives, from all growth hormone manufacturers, annual safety reports with specific focus on neoplasia.

So we will monitor for any safety concerns using our GeNeSIS program, spontaneous case reports that appear in our pharmacovigilance database, and any literature reports.

The second question that was asked is: "Will this new indication obviate the need for diagnostic evaluation in children with growth disorders?" This question was also raised by Dr.

Orloff. And the clear answer to this is that this will not happen, because this is the practice of pediatric endocrinology; this is what I as a pediatric endocrinologist and many of my colleagues do, is we evaluate the causes of growth failure. And this is what we're trained to do, and it's very important to do this because growth failure is a very key symptom that may indicate a serious underlying condition.

Furthermore, the peer professional societies under which we work--the Lawson Wilkins and the American Academy of Pediatrics--regularly provide guidance regarding diagnosis of growth disorders, and are likely to update their guidelines. And the insurance companies will require this work-up and statement of medical necessity before they will reimburse for treatment. And Lilly itself will enforce this, both through our label wording and through our educational programs.

The third question that was asked is: "Will approval for this new indication open the floodgates for inappropriate treatment?" There are a number of reasons why Lilly maintains that this will not occur. The first is the label that we

propose. The height threshold--I'll remind you--of minus-2.25 standard deviation excludes all children whose heights are in the normal range, and also excludes 46 percent of children with sub-normal heights below the minus-2 standard deviation score mark.

Second, the pediatric endocrine community does not want this to happen. Pediatric endocrinologists are relatively conservative and view themselves, in fact, as the gatekeepers of growth hormone therapy. The observational studies that Dr. Hintz showed indicate that they prescribe growth hormone quite conservatively across all indications, for heights that average around minus-2.8 to minus-3 standard deviation scores. Again, we expect the peer organizations will update their guidelines on appropriate treatment of patients with growth disorders. The insurance companies, again, will play a role here, because they will impose controls of their own, for their own financial reasons, and will continue to require a statement medical necessity before reimbursing treatment.

The final two features here are that Lilly has its controlled distribution process, and the

fact that we will market only to pediatric endocrinologists for this indication. These two factors will also limit the likelihood of any inappropriate prescribing.

But more than this, there are some intrinsic factors to growth hormone treatment that will help prevent this inappropriate treatment. Growth hormone treatment is not a small thing. Many decisions are required; many decisions must be gone through before a patient receives growth hormone treatment, and these decision steps will limit its use.

The first is the decision of the family to consult their primary physician about a concern regarding growth. The second is for that physician to refer the patient to a pediatric endocrinologist. The third decision point is for that endocrinologist to decide that the child has a disorder that warrants a work-up, because these work-ups are, in and of themselves, not small things; they're quite invasive, they require a half-day hospitalization in most cases. But, having done that work-up, the next decision point is for the endocrinologist to recommend growth hormone treatment to the family. The next decision

is for the family to accept that treatment--and that's not just the family, but the patient. And, finally, the decision of the insurance company to reimburse for that therapy.

So, with all these decisions in place, and the thought process, and the time that it takes to go through this, it is very unlikely that inappropriate treatment will occur.

But this may lead, then, to the next question as to: "With a new indication, how many patients with this condition will actually end up being treated?"

To address this we began by evaluating the prevalence of non-growth hormone deficient short stature as defined by our label wording--our label cut-off of minus-2.25 standard deviation scores. And by "prevalence" I mean the number of children in the U.S. today who fulfill these criteria. And this would be approximately 400,000 children between the ages of 7 and 15 years. And I should point out that this is only twice the number that is represented by an orphan drug indication.

Now, this 400,000 children are not all going to receive this treatment. In fact, once the various decision points have been gone through,

this will be significantly whittled down. So following the selective referral byprimary care physicians, the conservative treatment recommendations by pediatric endocrinologists, and the limited insurer reimbursements, we have projected that approximately 10 percent of these patients will end up on treatment at five years after approval, totaling about 30,000 to 40,000 patients across all brands of growth hormone.

So, to conclude, Lilly is committed to the appropriate use of Humatrope in this patient population, and a multi-level program will be in place to help manage any risks.

Having addressed now the rationale for treatment, the efficacy, the safety and the risk-management program, I'm now in a position to characterize for you the benefit-risk profile of treatment in this patient population. And to do this I will return again to the slide first shown by Dr. Enas, and address the last four questions that Dr. Enas raised.

First, "Are there ethical issues regarding growth hormone treatment of non-growth hormone deficient short stature?"

The first concern refers to a social

justice issue related to access to growth hormone therapy; that is, which patients should have access to this therapy? But we would point out that this is not unique to this indication. This is true for all of the other growth hormone indications and, furthermore, it's not unique to growth hormone as a drug but, in fact, refers to--could be referred to many drugs. And, indeed, an approved indication would provide more equitable access to patients across a broad range of socioeconomic groups.

The second concern raised is regarding resource allocation, and whether increased use of growth hormone will significantly impair the health care system from being able to take care of other health care needs. Here we point out that the growth hormone--that growth hormone itself accounts for a very small proportion of the overall health care budget, of less than .05 percent. So a slight increase in the use of growth hormone should not have any negative impact on the ability of the health care system to address other health needs.

The third issue raised has been whether the treatment effect adequately balances the cost and potential discomfort of treatment in this condition. However I would point out that this--basically,

this is a cost-benefit analysis, and this cost-benefit balance has been well accepted for the four other non-growth hormone deficient growth disorders for which Humatrope is currently approved, and there is no difference in this balance in patients with non-growth hormone deficient short stature and patients with the other non-growth hormone deficient growth disorders.

The fourth issue raised regarding ethics of this treatment is the difficulty in differentiating between normality and abnormality. This is something that pediatric endocrinology has struggled to deal with for the last 20 years, with respect to growth hormone stimulation test results, and which patients fall within the normal and the abnormal categories of growth hormone stimulation testing. So, again, this is not unique to this indication of non-growth hormone deficient short stature; and, furthermore, it's not unique to growth hormone either. For example, where does one draw the line between normal and abnormal blood pressure? This is constantly changing. And so this differentiation has been a situation in a variety of different conditions.

But Lilly has proposed an objective

criterion to help address this; and that is the label criterion that we've discussed--the minus-2.25 standard deviation scores. Pediatric endocrinologists, in evaluating the patients appropriate for treatment, weigh in many factors to determine who is appropriate, because they realize that normality and abnormality are not black and white, in life or in medicine but, in fact, form a continuum.

The final question--or the final issue raised--has been the potential for growth hormone to be used as augmentation therapy; that is, to be used to treat children whose heights are normal to make them taller, even though they're already in the normal range.

This is something that, as a pediatric endocrinologist, I'm well aware that my colleagues do not support. This potential has existed ever since growth hormone was first marketed, and this new indication will make no difference to that potential misuse of growth hormone. Pediatric endocrinologists do not support this type of treatment and, furthermore, the label restriction will eliminate patients whose heights are within the normal range. Our risk-management program that

I've already elucidated, also addresses this issue.

Having raised and discussed some of these ethical issues, the final question in this area is: "If there are potential ethical issues, who should address these?"

Lilly maintains that, assuming that the sponsor has established efficacy, safety and a positive risk-benefit, provides an effective risk-management program, and satisfies the FDA requirements sufficient for approval, that the most appropriate people--or groups of people--to evaluate any potential ethical issues are the pediatric endocrine community and the families of the patients themselves; and, further, that it is not ethical to exclude from growth hormone treatment children who are just as short as those currently approved for treatment, when the established risk-benefit is similar.

The next question asked is: "Is it appropriate to treat patients whose short stature is not clearly associated with a defined disease?" And here I'll return to a point that Dr. Hintz made elegantly in his presentation, is that many conditions that deserve and receive treatment may not be accepted by everybody as diseases. And

listed here are a number of such conditions. Listed in Dr. Hintz's slide were other such conditions. This is not a relevant question with respect to the appropriateness of treatment.

Growth hormone treatment and, in fact, the label indications for growth disorders, indicate that we are treating the growth failure or the short stature associated with various conditions, but not the underlying condition or the disease. For example, growth hormone has no impact on any other aspect of patients with chronic renal insufficiency or Turner's syndrome beyond their growth. We are simply treating their growth failure and their short stature. And the growth failure, as we have reiterated--the growth failure in this group of patients is very similar to that seen in patients with other growth disorders.

The next question raised is: "Should psychological or quality of life benefits be required outcomes of growth hormone treatment?"

While this is a relevant question, I would point out that this has not been conclusively demonstrated for either growth hormone deficiency or for any other growth disorder that is currently approved for treatment. And this has not been

required for growth hormone approval for any other growth disorder. And, furthermore, when the Endocrinologic and Metabolic Drugs Advisory Committee gave their recommendations back in 1987, they did not specify benefits other than growth as required outcomes of treatment.

Finally: "What is the clinical relevance of the efficacy?"

Most patients reached normal height during childhood. Similar growth improvement was seen to that in other indications, and similar final-height benefit was seen to patients with Turner's syndrome. Eighty-two percent of final-height patients in the higher-dose group gained at least one standard deviation score in height, and this is equivalent to two-and-a-half inches at adult height. Sixty-two percent of the final-height patients in the higher-dose group gained more than two inches, and 31 percent gained more than four inches over their baseline predicted height; and 94 percent of patients in the higher-dose group were in the normal range of height at their final height.

So what this effectively does--this height gain--is to start to shift patients from this

distribution to this distribution, and thereby to trim back some of this gap in height that exists between the average-statured population and those with non-growth hormone deficient short stature. And with this change in height, and with this improvement in height, what are the potential outcomes?

Well, I return again to a slide similar to that shown by Dr. Hintz, where we listed a number of the potential disadvantages of short stature. So what the treatment may have the opportunity to do is to prevent this boy from being constantly treated as a child three or four years younger than his best friend here, and to prevent him from being excluded from many peer activities. And in adulthood, this treatment might provide the opportunity to this woman to buy clothes off the rack at a regular store, as opposed to having to buy children's clothes, or have them altered; may allow her to obtain a job that she would otherwise have been ineligible for due to the height restrictions; and may provide her the opportunity to sit the requisite 10 inches away from the steering wheel that is required for air bag safety.

So to conclude the benefit-risk

assessment, these last presentations have demonstrated that Humatrope is clearly effective and safe for the treatment of non-growth hormone deficient short stature, and that a dosage of .37 mg per kg per week confers greater benefit, without evidence of increased risk. Therefore the benefit-risk profile of Humatrope in non-GHD short stature is favorable, and is similar to that in other approved indications.

And this now allows me to conclude with the eight reasons why this committee is asked to recommend that Humatrope be approved for patients with non-growth hormone deficient short stature.

First, these patients are as short, and as deserving of treatment as those with current indications.

Second, recognizing the unmet medical need of these patients, the 1987 Endocrinologic and Metabolic Drugs Advisory Committee recommended a placebo-controlled study to final height; a truly rigorous gold-standard study.

Third, the pivotal study that was run by Eli Lilly and Company and the NIH used this rigorous recommended design to run a study over 13 years, taking patients to final height. And a

study such as this will never be repeated.

Fourth, this pivotal study demonstrates unequivocal efficacy in this patient population. The supportive study demonstrates a greater benefit at a higher Humatrope dose. There is consistent efficacy across the published literature and Lilly studies. The efficacy is clinically relevant and is similar to that in other conditions. And, finally, the safety is similar to current indications.

The benefit-risk balance therefore justifies approval, and there now remains no valid scientific, medical, regulatory or ethical reason to withhold treatment from these patients.

And I'll now hand the podium over to Dr. Margaret MacGillivray for some concluding remarks.

Concluding Statements

DR. MacGILLIVRAY: Dr. Braunstein, members of the Advisory Committee, members of the FDA and guests.

My experience with human growth hormone began in the early 1960s when pituitary-derived growth hormone first became available for clinical use. Over the past 40 years we have learned a great deal about the benefits and risks of growth

hormone therapy. Growth hormone treatment is effective and safe for children with growth hormone deficiency. It corrects their height deficit in childhood and renders normal adult heights.

When the FDA approved recombinant growth hormone in 1985 for the treatment of growth failure in children with growth hormone deficiency, they did so without requiring a placebo-controlled study or requiring long-term adult height outcome. However, they did mandate that a post-marketing surveillance study containing safety and efficacy data be contained in a database, and that database--the National Cooperative Growth Study--has tracked more than 40,00 children on growth hormone treatment, and the cumulative exposure for growth hormone in this population is 113,000 patient years. Few other drugs in the history of therapeutics has had such close scrutiny.

On December the 10th, 1996, I recommended to the FDA advisory committee that approval be given for recombinant growth hormone to be used to treat the short stature of Turner's syndrome. And this approval was given, even though these children do not have growth hormone deficiency. Final-height outcome data was provided in this

population, and this was the first approved indication for which adult-height data was given as a proof of efficacy.

At the present time, FDA has approved treatment of growth hormone for three additional non-growth hormone deficient conditions: chronic renal insufficiency, Prader-Willi syndrom, and children born small-for-gestational-age with persistence of poor growth. The approval was given in each of these conditions without considering the growth hormone secretion status of these patients, and without requiring long-term outcome data or placebo-controlled trials.

Five-and-a-half years have passed since the FDA gave approval for growth hormone treatment in girls with non-growth hormone deficient Turner's syndrome, and today Lilly has presented on the efficacy and safety of growth hormone in severely short but otherwise healthy, non-growth hormone deficient children. The etiology of the growth deficit in this population has not been defined, but it is apparent that these children do respond favorably to growth hormone treatment.

What are some of the arguments against treating these children with growth hormone? They

do not have psychological decompensation, and therefore they do not need growth hormone treatment. However psychological decompensation has never been a prerequisite for treatment in growth hormone deficient children, or in any of the other approved indications of non-growth hormone deficient short stature groups. These are healthy children, and their normal peak growth hormone response to growth hormone stimulation tests mean that they do not need growth hormone treatment. However, we know that growth hormone stimulation tests are not the gold standard for evaluating growth hormone secretion, and they do not predict an individual child's response to growth hormone therapy.

This line of reasoning is also invalid because these children do not spontaneously correct their height deficits and reach normal adult heights. And this was shown in the placebo arm of Lilly's pivotal trial, and also from abundant observational study data in the literature. In a large sub-study within NCGS, non-growth hormone deficient short children who were not treated, versus those who were treated, showed that the not treated group did not grow more rapidly, and they

did not improve their height SD scores, whereas the children with growth hormone treatment did improve their height SD scores. And when this data was compared to the growth hormone deficient population who were not treated, versus treated, the similarities in these two groups was striking.

The evidence presented today by Eli Lilly on the pivotal double-blind, randomized, placebo-controlled trial to adult height shows unequivocally that the treatment is efficacious and safe in non-growth hormone deficient children with significant growth failure. Further supportive information came from Lilly's dose-response study using larger doses of growth hormone, and showed that these children had greater height gains and better height outcomes.

Additional evidence came from the meta-analysis of Finkelstein and colleagues, who shoed that using global studies of controlled and uncontrolled populations of children treated with growth hormone, that the treatment was efficacious.

The efficacy information from the NIH pivotal study is particularly meaningful because the dose of growth hormone in the trial was sub-optimal, and it was given three times weekly,

rather than daily. Furthermore, the late age--12-1/2 years of age when these children started growth hormone therapy--was not ideal, because many participants were peri-pubertal or pubertal, thereby shortening the effective treatment time.

Non-growth hormone deficient short stature is not a new condition. It wasn't invented by pediatric endocrinologists or by growth hormone manufacturer. In my over 40 years of clinical practice in a regional referral children's hospital, I have seen hundreds of these children whose families come seeking help so that they may be freed from teasing and being mistaken for children younger than their actual age. They want the opportunity to have height in the normal range during childhood and during adulthood.

The growth disorder in these non-growth hormone deficient growth-delayed children is effectively and safely treated by growth hormone treatment, as shown by Lilly. Ninety-four percent of the treated patients reached adult height in the normal range. The evidence p resented today indicates that these children should have the same access to growth hormone treatment that is currently available to other groups of non-growth

hormone deficient short children.

I will end by showing a video of a former patient of mine who came when she was 2.8 standard deviations below the mean for age, and her peak growth hormone was 16 nanogram per mil. On growth hormone treatment she reached a height of 5'3", and in the interview she discusses how she felt before receiving growth hormone treatment and what the treatment did to change her life.

[From video]

PATIENT: You know, you can blow it off when it's just your older brother making fun of you, but my friends and my peers were always saying, "Oh my God, she's so short," and "Oh, you're not old enough to be hear," and like normal people that I passed on the street, or, you know, when I was shopping in the mall didn't take me seriously.

It's such a drastic change. It helped in my self-esteem. I could do sports, I could join sports team. I'm now a lifeguard, which I probably would never have been doing before.

DR. MacGILLIVRAY: The comments made by her does show the clinical relevance of the treatment, in terms of what it meant to her life.

In conclusion, as I did in 1996 for Turner's syndrome, I again recommend to the advisory committee and the FDA that approval be given for Humatrope to be given an indication for non-growth hormone deficient short stature children who have significant growth failure.

Thank you.

DR. BRAUNSTEIN: Thank you for a series of very enlightening presentations.

We'll now take a 15-minute break and then reconvene for questions.

[Off the record.]

DR. BRAUNSTEIN: Back on the record.

We'd like the committee members to take their seats, please.

[Pause.]

Committee Discussion

DR. BRAUNSTEIN: Well, we'll start with asking committee members to pose questions to Lilly, based on the presentations and the documents that they've received.

Dr. Woolf?

DR. WOOLF: I would like to address some of the psycho-social issues that have been raised. In the briefing documents some of the information was

actually in the very extensive bibliography that was sent to us. But it's a little bit, I think, in conflict to what we've heard. And there was a paper from Children's Hospital in Buffalo, looking at the psycho-social screening project in 258 children.

The conclusion was, "These findings suggest that despite the presence of negative psycho-social experiences related to short stature, these children are functioning generally well. The effects that these stressors exert are likely only contributing to variability in psycho-social functioning that falls within the normal range."

So I have a few questions relating to this issue.

As an adult endocrinologist, I'm not really sure--what is a clinically significant increase in height? Is it one inch, two inches, five inches, eight inches? I don't know.

What age should growth hormone treatment be started, if we're going to approve it? Should it be started at age three, five, eight, 10? Any time before puberty?

And, finally, what is the evidence that if these children do have psycho-social problems that

treatment with growth hormone and improvement in their height will reverse these problems?

DR. BRAUNSTEIN: Dr. Cutler?

DR. CUTLER: Yes. I think that--let me begin with the first one, the question of a clinically meaningful difference in height. I'm not sure there's a perfect number you can give. It may be different for each child. This may be something where our consultants can help on this, and it may matter where you are. For example, if you're 4'9", for example, being 4'10-1/2" will actually allow you to get certain jobs that you couldn't have gotten, or may allow you to drive a car safely, for example--4'11". So an inch-and-a-half can be meaningful, depending on where you are in the height range.

And certainly, I think that the mean treatment benefit of three inches, which was what was seen in the higher dose arm, is, I think, a quite meaningful benefit to most patients. And if a patient doesn't feel like that level of benefit would be meaningful, this is a patient who probably--you know, and this is the kind of thing that pediatric endocrinologists do in real-life practice, is they have a risk-benefit discussion

and will make a judgment. And that's one of the reason that some children elect not to be treated. They feel that the benefit-risk, or whatever, for them is not where they want to go.

The second point, about age: this is really, I think, a matter of clinical judgment. We looked at age as a predictor. And right out to the maximum ages of children enrolled in both of these studies, we didn't see any decrement in benefit. There was a decrement in the height over predicted height, but that was also true for the placebo group, which tended to catch up somewhat. And so when they were older they caught up last. The Humatrope exceeded their prediction by last, but the net difference between them didn't really change up to at least an age of about 15, or a bone age of about 13. So we didn't see, up to the ranges in this protocol, any age, and that included children who were up to as far as Tanner stage 3 of puberty--although there were very few children at that point.

So--and in terms of a minimum age, children are rarely, for a variety of reasons related to all these decisions, treated much earlier than five, which was the lower age in our

E001 study, and the majority of patients, the mean age, really, of treatment I think in the observational studies is more like nine or ten.

Psychological data--there were psychological data collected in this study, but it was decided at the time that Lilly and the NIH decided to work together that the NIH would be responsible for collecting an analyzing those data. They were not on any of the Lilly case report forms; they're not in the Lilly database.

Now, the NIH has collected them, and Dr. Judy Ross actually is here, from Philadelphia. She was the principal investigator of the Philadelphia site, and could give you a several-minute overview of the outcome of the psychological data from this study, if you would like--or I could give you just a very high level summary. Really, it's your discretion--depending on how important it is to you.

DR. BRAUNSTEIN: Why don't we have Dr. Ross give that presentation.

Dr. Ross?

DR. ROSS: Well, I'm very pleased to be here and have an opportunity to go over this data with you.

I'll remind you, this is the results of self-image and behavior questionnaires collected as part of the GDCH study. This was the placebo-controlled, randomized trial that was done by both Eli Lilly and NICHD in conjunction.

As part of this, two questionnaires were utilized. One was the self-perception profile. This was a child report completed by the child at the visit. It assesses domain-specific judgment of confidence and perception of worth.

The second questionnaire was the child behavior checklist. This is a parental report, completed by, usually, the mother at the visit. It assesses behavior problems and social competencies in several sub-scales.

These questionnaires were distributed to the child and the parent at baseline and yearly. And the statistics that I will report to you are t-tests done year-by-year across the treatment groups.

Now, first off, there's some controversy in terms of the literature, but in our hands, in this study, the results of the self-perception profile and the child behavior checklist were normal at baseline. I'd also like to add that

these are instruments that are widely used both in the United States and Europe. The child behavior checklist has been available since the 1970s, and is one of the instruments that was reported by Dr. Sandburg in the Buffalo Review that Dr. Woolf just referred to.

So this shows you the baseline results from the child behavior checklist--and I have three summary scores, each of which encompasses several of the sub-scores within this test. And they are reported as t-scores, which means that the average, or the mean, is reported as 50, and the standard deviation is reported to be--is normalized to 10. So this is a standardized way of reporting this data.

And, as you can see, the placebo group and the Humatrope group were normal at baseline and really quite comparable to each other.

So these are our treatment results. For the self-perception profile, the child questionnaire, there was no difference between the Humatrope and placebo-treated groups during the four year treatment interval. In contrast, for the child behavior checklist--the parental questionnaire--the Humatrope group had improved

scores on the problem behavior summary score, the externalizing summary score, and the internalizing summary score at the four-year treatment interval, compared to the placebo group. And I'll be telling you a little bit more about these.

First, the child behavior--the problem behavior total sub-scale. This is a summary score reflecting eight component scales. And they include social problems, anxiety, depression, somatic complaints, etcetera. And, again, as I told you, it's reported as a standardized t-score with a mean of 50, and one standard deviation being 10. And in this particular case, a higher score indicates more problem behaviors.

So, this is the first result--the problem behavior total. And here on the y-axis is the change in score from the baseline value obtained. And so a change of 10 is equal to one standard deviation score. And so this is really a substantial effect size.

This is the year in study--one, two, three and four. The Humatrope group is shown in green; the placebo group is shown in pink. And these are the numbers within each of those groups, according to year.

And these are the p values for the t-test done year-by-year, across the groups. And so, as you look at this first one, you can see that at one and two years there was not much change or difference between the two groups. By years three and four, there's greater separation, where the placebo group has a rise in score, and a worsening of their problem behavior profile.

I would add that these results are reflected by the components, which either also showed statistical significance, or no significant change. I would also like to add that at the zero point, the mean age was about 12-1/2, and by three years, where we're starting to see a separation between the placebo and the control groups, they're about 15-1/2 on average, and well into adolescence.

The next summary score is the child behavior externalizing sub-scale. This is also a summary score of under-controlled type problem behaviors, and it encompasses the delinquent and aggressive sub-scales, and includes acting out or aggressive behaviors. And this shows you again the change in score versus the year in study for our two treatment groups. And for this externalizing summary scale, it looks very much like the total

problem behavior scale, with differences beginning to emerge at three years and four years that are significant at p less than .05.

And the last one I will show you is the internalizing sub-scale. And this is, again, a summary score in the child behavior checklist, encompassing the withdrawn, somatic, anxiety and depression sub-scales. And this is related to internalizing-type behaviors, excessive worrying and depression. And I show you, again, the internalizing behavior total; the change in score versus the year in study for our Humatrope versus placebo groups. And you can see, again, similar changes emerging at the third and fourth year into the study, when they are well into adolescence.

Now, these results are inconclusive, and there are several reasons for it. First, the small sample size--and you could see from the numbers that, by the fourth year, the numbers had really started to drop off, in terms of the available evaluable data.

There was missing or incomplete data on the questionnaires, which eliminated them from being included in any kind of analysis. There may have been a drop-out bias, in terms of who

completed these questionnaires, and the psychological data that we did have available.

There was no correction for the multiple comparisons and the multiple sub-scales. And I didn't show you this, but there was no correlation with change in growth rates or height SDS when we looked at it from that vantage point.

But I would summarize by saying that these results are unique, because they control for placebo effect, which can have tremendous impact on self-image, or psychological results. It eliminated any kind of study participation effects and placebo effects. I think on the basis of what I've shown you, we can safely conclude that growth hormone does not deleterious effects on self-image or behavior.

And, last, there was a trend towards positive growth hormone effects on problem behaviors, externalizing, and internalizing behaviors in the child behavior checklist.

Thank you. And I'd be happy to take any questions.

DR. BRAUNSTEIN: Thank you Ross.

Dr. Woolf, is that--

DR. WOOLF: It answered my question.

DR. BRAUNSTEIN: Thank you. Appreciate it.

Yes. Dr. Grady?

DR. GRADY: I'm basically just trying to get this straight, in terms of what we're asking ourselves here. And just--I just want to ask you if it's correct to assume that we're really talking about treating short stature in kids along about the age of 10, to make them taller along about the age of 17 or 18. And we're talking about defining that in kids whose height is more than 2.25 standard deviations below the mean, which would encompass one in a hundred of every kids. Is that right?

And our best estimate of what this effect is going to have is probably to increase their height, perhaps on the order of one-and-a-half to three inches. So they're going to go from what we'd estimate here as something like 4'10" in girls, and 5'3" in boys, up to something like 4'11--up as far as 5'1" in the women, and in the boys, from 5'3" up to maybe 5'4" to 5'6"? Is that right?

DR. CUTLER: Well, there is one additional--it's close to being correct, but the final heights that we've given you are the gain over placebo, essentially, in the pivotal study. And there was

some gain of the placebo patients who were untreated, which corresponded to probably about an inch, if you really looked at it.

So, there's some gain in this group because they have a bone-age delay, so that the actual final heights might be another inch or so. But that's very close.

Essentially what you're saying is correct, but if you remember the height SDS increase, when I showed you it temporally, by year-on-study, there was an increase in height SDS for the placebo group as well. So if you don't add that in to the baseline starting height, you'll end up with a little shorter height than you would be getting.

So someone, for example, who's 4'9", who would have ended up at 4'10", for example, without any treatment, now ends up at either 4'11-1/2" if they use the low dose, or 5'1" if they use a high dose--higher dose.

DR. GRADY: Ahh--okay.

DR. CUTLER: On average--and that's just a--that's obviously the mean result for the population.

DR. GRADY: My other question--I mean, I'm

trying to get an idea whether--I think in some ways it might make a difference whether they gain one inch or three inches.

What was compliance like in your pivotal study?

DR. CUTLER: It was 84 percent for the placebo group, and 88 percent for the Humatrope group, based on compliance diaries, where they kept a record of every injection.

DR. GRADY: And I'm assuming they had a lot of support for compliance; that they had study visits, physician seeing them fairly frequently--all of that sort of thing that happens in a trial?

DR. CUTLER: It was a highly selective group, and we certainly tried to reinforce compliance at each six-month visit. But these patients were coming from all over the country to the NIH, and we basically really didn't see them in the six months between. We obviously hoped that they were complying, but there was rather little we could do, other than at each six months we would re-emphasize the importance of compliance to get a meaningful outcome.

DR. GRADY: And am I also correct in thinking that compliance--two things. I mean, I

think that the shorter--it seems to me, from looking at this stuff, that the shorter the height to begin with, the greater the effect. And, of course, the inverse of that is that the taller the child is to begin with, the less the effect, so that compliance and baseline height have a fairly important effect on the final result?

DR. CUTLER: Umm--I'm not--could you clarify how you came to the conclusion about baseline height? Because I'm not sure that baseline height really has much effect on the incremental gain above where they started.

DR. GRADY: Basically, looking at the height--you know, the predicted height increases from multiple studies, it just seems like the shorter the kid is to begin with, the more the effect.

So you didn't do that in your study? You didn't look at baseline height as a predictor of effect?

DR. CUTLER: We have looked at it, and it was not statistically significant. It was--the correlation coefficient was .25, and so the--and the p value was .26. And so it really explained a pretty small amount of the variance--maybe 5

percent--6 percent, I guess.

DR. GRADY: Okay.

DR. BRAUNSTEIN: Dr. Cara?

DR. CARA: A couple of questions.

Can you explain what you just said about the final height actually being a little bit more than the placebo group?

DR. CUTLER: Ahh--yes. These patients often have some bone-age delay, and so if they come in with a baseline height SDS of minus-2.8, they might have a predicted height of minus-2.3 or 4, for example. And, in fact, you may remember that at baseline the placebo patients had a mean height SDS of minus-2.8. But without any treatment, they ended up at minus-2.3. And that really is a little bit of catch-up related to their bone-age delay and the fact that they really have a little bit more time to grow because of the bone-age delay.

DR. CARA: But there was no real difference between the predicted height SDS and the final height SDS.

DR. CUTLER: That's right. That's right. In other words, they were minus-2.8 at baseline, minus-2.3 when they finished, and their predicted might have been just a tad above that. They were

just lest than a centimeter below their mean predicted.

So they did have a predicted height that was higher than their baseline height SDS, factoring in that bone-age delay that's often seen in this group.

DR. CARA: Another question is related to your intent to do a--or your desire to do an intent-to-treat analysis in the pivotal study. If you look at your slides--and I'm looking specifically at slides--let's see here--

[Pause.]

--the final-height population versus the efficacy evaluable population, in terms of their final-height SDS. The efficacy evaluable population ends up being about .3 SDS taller than the actual final-height population. I'm looking at slides number 61 and 62.

DR. CUTLER: Okay.

DR. CARA: Now, usually in an intent-to-treat analysis, the intent-to-treat analysis versus the actual protocol completers is generally downplaying the effect of therapy. But here it's actually enhancing therapy.

How can you explain that?

DR. CUTLER: Yeah--I'm not sure that I have the same slide number that you have. Is this--

DR. CARA: Sorry, it's 41 and 42.

DR. CUTLER: 41 and 42--okay.

DR. CARA: So this is the final-height population--

DR. CUTLER: Right.

DR. CARA: --and the final height is minus-1.8.

DR. CUTLER: Right.

DR. CARA: And then if you look at the next slide--

DR. CUTLER: Right.

DR. CARA: --the efficacy evaluable population--

DR. CUTLER: Right.

DR. CARA: --the height SDS at 18 years for the Humatrope treated is minus-1.5.

DR. CUTLER: Right.

DR. CARA: Now, these are presumably kids that have either completed the protocol, gotten some growth hormone and dropped out, or got one dose of growth hormone and dropped out. Is that correct

DR. CUTLER: Right. This is--well, this is

the efficacy evaluable population first--and I probably will defer in a moment to our statistician if need be--but in this analysis, this is people who were treated at least six months. And so they had, in the Humatrope group, they had at least six months of treatment, and then wherever they--you know, and then they dropped out at variable points between there and final height.

Now, because this is efficacy evaluable, this includes the final-height patients. So the final-height patients are in this analysis, and the non-final-height. So you can sort of think of the efficacy evaluable as having two sub-groups. I had a lot of tripartite slides. One sub-group is the final-height, the other is those who didn't make it all the way to final height. This is a combined analysis of both, and the repeated measures approach basically models the ones who didn't get to final height based on ones who did, and projects where they would have ended up.

So it is not--not all of these are measured. This is a combination. If they were at final height, this is a measured--you know, or if they went to 18, if they had a height past 18 this is a measured height, but if they didn't get there,

it's what they were projected to by the repeated measures analysis.

DR. CARA: I see. And actually what you're saying--that it includes two populations. It actually--

DR. CUTLER: Right.

DR. CARA: --it actually includes three populations. It includes the patients that were treated for a minimum of six months and then dropped out--

DR. CUTLER: Right.

DR. CARA: --patients that were protocol completers--

DR. CUTLER: Right.

DR. CARA: --and then patients that were no protocol completers, but--

DR. CUTLER: --came back for a final height. Right.

DR. CARA: And the final-height slide that you show, it's slide 41, I believe--and then again, in the slide that shows the individual data points--although I don't know if you had it for this study--can you give me an idea of where the actual protocol completers were, versus the non-completers?

DR. CUTLER: Yes--and just give me a second

and see if I can--either I or our team can give you an analysis that looks like this.

Well, let me tell you that the protocol-complete--simply to summarize--the protocol-complete results look quite similar to the final-height population, because it's mostly protocol-complete patients. So it had an effect size. It was a little bit smaller. It was .46 SDS versus .51 for the final-height population, but very similar effect size between the final-height population that you're seeing on 41.

The difference between this--and if you didn't look closely at it, the protocol-complete population will look very similar to this, except the effect size is 0.46, which is about 10 percent less.

DR. CARA: And then a related question, related to the supporting study--the E001 study--a similar trend, I think, is shown in the slide--let's see, slide 53, I believe, showing the secondary analysis; the two year height-velocity population where, again, it seems that the two year height-velocity population actually, in the long run, do better than the final-height population.

DR. CUTLER: Yes. Maybe--you know, it

might--I will--let me take a moment to do this, and if--again, if you're not satisfied with my ability to explain this, I'll be happy to get our statistician to do it as well.

These are sort of two complementary analyses. And I'm happy to explain these, because I had to be taught what they are. And we'll see if it works.

Here what's done is the last observed height SDS. If it's a final height, it's the actual final height. But if it's a dropout--and it could be, in this case, a dropout at six months--we take whatever the height SD was at the very last observation, and then you simply analyze it. So they're all observed.

DR. CARA: Can I just interrupt you for just one minute?

DR. CUTLER: Yes.

DR. CARA: And in your protocol--your--what am I trying to say?--in your placebo group, if anything, you showed that the patients actually did better than that--in the long run. If you took their SDS and assumed that they continued at that SDS all along, their final height was actually a

little bit better than that; about an inch better.

DR. CUTLER: Well, it's about an inch better than where they' started but, remember, they started at minus-2.8, and the placebo patients ended up at minus-2.3 in the final-height population, and minus-2.4 for the last observed height.

DR. CARA: So what you're doing here--if I'm understanding you correctly, is you're talking the SDS at the last observed height--

DR. CUTLER: Right.

DR. CARA: --and then following it through--

DR. CUTLER: Carrying it forward, in a sense. Right.

DR. CARA: --carrying it forward--

DR. CUTLER: Right.

DR. CARA: --assuming that they would stay in the same SDS. But, in fact, your placebo group ended up a little bit taller than that.

DR. CUTLER: Right. It's--this is often called a "last observation carried forward" approach. That's exactly right.

DR. CARA: So why is it that those patients do better than the actual patients that completed

to final height?

DR. CUTLER: Now, which group? Better than the placebo?

DR. CARA: No--better than the Humatrope-treated patients that completed final height.

DR. CUTLER: Umm--well, I think if we--maybe we should--the final-height population for this group is shown--

DR. CARA: I think it's the slide before.

DR. CUTLER: It's like one of the 60's or so. Well, the final height for the dose study, for this--this group is minus-2 for last-observed. Do we have the final height? It's about slide 60 or something like that. It's the one where I summarized the final height SDS for the two studies.

DR. CARA: Yes, it's slide 58, I believe.

DR. CUTLER: 58, maybe--if we go back--yeah.

So, no--yeah, okay. So that was about minus-2, but the final height is minus-6. So the last-observed height was down here, and the actual final heights were about minus-1.6. So it was somewhat better than--the ones who were followed all the way through on the .24 dose were better

than the ones who were just last-observed.

DR. CARA: But if you look at the higher dose, they ended up at minus-0.8.

[Pause.]

DR. CUTLER: Okay. Yeah, we need to--

DR. CARA: And the lower-dose ended up at 1.3 when measured at 18.

DR. CUTLER: Yes. Can we go to the next slide?

DR. CARA: So I'm not quite sure why you're saying they ended up better?

DR. CUTLER: Oh, you're thinking about the repeated-measures analysis now.

DR. CARA: Right.

DR. CUTLER: Can we go back to about--to the earlier one?

DR. CARA: Slide 63?

DR. CUTLER: I'm trying to understand--are you concerned about the slight differences in the numbers on these different--and what they really mean on the different analyses? Or--

DR. CARA: No. I'm looking at the fact that the height SDS at 18 years--

DR. CUTLER: Right.

DR. CARA: --was better for the--

DR. CUTLER: Repeated measures.

DR. CARA: --repeated measures than it was for the actual treated.

DR. CUTLER: Right. And it is a model. It's a statistical model that is modeling some for whom we don't have final heights--

DR. CARA: And based on your placebo data, if anything, this model is actually under-predictive of final height.

[Pause.]

DR. TAMBORLANE: What I think Dr. Cara is referring to is that with prolonged treatment, over time, at the high dose, you may actually start losing a little final height. If you--you know, when you--because normally, if you're taking the last observation carried forward, you're not seeing the true drug effect with the low dose you see that. You don't see the full drug effect until the final height measurement.

But, in this case, you're saying that you see a projected last-observation carried forward which would be .8. But when you actually look at the actually people who get to 18, it's 1.2.

DR. CUTLER: Yes, well, let me--that's the point.

DR. TAMBORLANE: I mean, obviously they're different subjects, and that may be just--

DR. CUTLER: Yes.

DR. TAMBORLANE: --you know, a subject effect. But it's an interesting idea.

DR. CUTLER: Let me summarize these numbers. It's hard to do. We haven't put them all on one slide. And I'm not sure I can interpret them, but let me just reiterate, then.

So, the last observation carried forward for the higher dose gives a last-observed height SDS mean of about minus-1.4. If you actually look at the actual mean final heights--this is now 48 patients. Of the 17 patients who got to final height, it's a little bit higher at minus-1.2

If you now take the ANCOVA model, which requires having a baseline predicted height, four of those 17 were too young to have a baseline predicted, so they get dropped out. And with the 13, and an ANCOVA output--the output of the ANCOVA, a final height SDS for this group is minus-1.0. And the repeated measures analysis, which estimates--takes both measured and then, in a sense, project heights based on the trajectory--and even if it's a trajectory going up and down, the

repeated measures essentially will try to mimic that, whatever it was, for those who got to final height, it's minus-0.8.

So, in a sense, what you're pointing out is that there were different estimates of where this group ended up, based on different numbers and different statistical analyses, ranging from about minus-.8 to minus-1.2. And beyond that, I think they're somewhat different approaches statistically, and they involve somewhat different patients. And that's probably about the best we can say about where these patients really are likely to have ended up.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: I'm convinced that there are gains in height that are significant with this treatment, but I have some conceptual questions about the use of the standard deviation scores.

One is that it's a potentially moving target. As people--the general population get taller, the mean will change, and the variability around that mean may also change. So if the average in the population is taller but the variability is greater, the standard deviation score may stay the same. That's sort of a comment.

The question is, in looking at the growth chart that Dr. Hintz showed earlier, there's a spread that changes from pre-adolescence, through adolescence to final. And I deal with this regularly in looking at bone density, where we think about z scores. And if you look at the variability around the mean at age seven, it's very tight, because most seven-year-olds are very close to the mean.

If you look at age 12, it's pretty wide. And so a 12-year-old may actually be further away from the mean, and yet have a better standard deviation score simply because of the variability being greater in the population at that age.

So is there some artifact in this SDS score that might particularly affect the last measure carried forward, where if you're calculating the SDS score at a time when the variability in the population is great, you're carrying forward a better score.

DR. CUTLER: Well, your points are very astute, and particularly for a non-pediatrician. I mean, this is exactly right--all of these points.

But they are pretty subtle. And I think all I can say is it's one way to do the analyses.

It seems to be the one that pediatric endocrinologists prefer as having the least problems of all the various ways they can go about it. But I think your points are correct.

Maybe if you had given me the growth chart--I'm willing to show this again, just as a refresher. Because I think it is true that standard deviation, first of all, tends to increase somewhat with age. And over the age range of these studies, which is pretty much from--I mean, we had some children as young as five, but the mean ages were about nine to ten; for the dose-response, about 12.

From here on through to adulthood, there is a gradual increase, but it is not an enormous change in standard deviation score. It seems to be--you know, it's pretty well behaved, I guess I would say. So it doesn't--I don't believe, as best we can tell, at least to anything that's misleading about the data, it might help explain some of the very minor inconsistencies that you're picking up between the different analyses, going .1 or .2 SDS one way or the other.

DR. BRAUNSTEIN: Dr. Follman was next.

DR. FOLLMAN: Yes, you showed a slide

earlier--slide 46--which shows the trends in SDS in the pivotal study. When I looked at this I was struck by what happened in the placebo, which shows an increase. And I sort of think, you know, if you're at the 3rd percentile today, you should generally track and stay around the 3rd percentile as you get older.

That's not being shown here at all in the placebo group. You show an increase of about a half an SDS.

Now when I saw this, before your presentation today, I was wondering if this might be due to sort of a dropout bias, where patients who are not improving so well don't show up later on. And that's a bit of a concern for me, but I've had--I looked at the data more thoroughly, and I've had discussions with the FDA and I think, in terms of the dropout--in terms of the treatment effect, I'm willing to accept an estimate of, say, an inch-and-a-half in the study.

However, you pointed out that perhaps a reason for this increase was not dropout but this is just what happens with SDS in short stature children. Is that your basic point?

DR. CUTLER: Yes, I think this is not

primarily a dropout bias. This is--and it's one of the reasons why it's very important to have a placebo-controlled trial. These patients tend to have a little bit of a bone-age delay, and they do catch up somewhat in height standard deviation score. They don't say exactly had the same height standard deviation score.

DR. FOLLMAN: Well, this made me think of another issue, which is in your labeling you aren't proposing a chronological age, it's just based on the SDS. And so if you have a young person, maybe seven years old, or five, which, you know, was included in the E001 study, they might have a low SDS, which perhaps it's not calibrated so well at this end of the spectrum, and with two or three years' waiting might increase their SDS some. That's what we're seeing here.

So, this raises an issue about not having a chronological age cut-point for this indication, when there's evidence here that the SDS is not stable, and that it increases over time for these children; these short children.

DR. CUTLER: Well, I think this is one of the--the key thing about your observation is, I think, an important one. I mean, pediatric

endocrinologists do not want to treat children who are going to end up at a normal height without treatment. And it's one of the things that they spend, you know, three years of intensive training trying to learn how to do. It's not perfect. But there are factors, like predicted height and so forth--how short they are--and many of us will actually, if we're uncertain about what the progress is going to be, will follow a child for some period of time before making a definite decision about treatment.

I think the purpose of the--what you're suggesting is the idea that the cut-off ought to somehow be age-dependent. I think that would become very complicated. And this is effectively, I think, a way to select a patient population within which pediatric endocrinologists can appropriately make further decisions about who should be treated and who not to be treated.

DR. FOLLMAN: Well, I wasn't really thinking of an age-specific SDS score necessarily, but just--I was concerned about the same phenomenon you were talking about that they might, you know, show improvements if you wait a little while, and basically not need the therapy. And you're not

really requiring that in your proposed label.

DR. BRAUNSTEIN: Dr. Tamborlane?

DR. TAMBORLANE: I have one for Dr. Quigley.

So seemed to implicate that there wasn't evidence for insulin resistence with growth hormone treatment. Do you really believe that a dose of .375 mg of growth hormone per kg per week is not going to reduce insulin responsiveness?

DR. QUIGLEY: We did not see any evidence for insulin resistence in the placebo-controlled study. We don't have the data in the .37 study, but what we do have is data from our registration studies in Turner's syndrome, which used quite similar doses. And so--

DR. TAMBORLANE: Similar to what? 3.7--

DR. QUIGLEY: Yes--.27 and .36--if I could have the Turner's syndrome insulin data--and what we saw, at least in fasting insulins--we don't have the QUICKI analyses, but in the fasting insulins we saw no differences across the different doses in this study.

So this was our registration trial, and here we see the baseline values, which are not particularly what you're interested in. But here

at 18 months--this was a placebo-controlled study--at 18 months we see no differences in the fasting insulins between the dosages groups, or between these groups and the placebo group. So at least up to that level--up to about .37, in a population that's already more insulin resistant than we expect these patients to be, I don't think we would see a differential dose effect.

If you go all the way up to something like .7, you might.

DR. TAMBORLANE: But--I mean, one of the problems with using the fasting insulin as your marker, I mean it may actually be relatively--a good marker in severe insulin-resistant states like obesity and things like that. But--I mean, there are data that suggest that growth hormone is primarily affecting peripheral glucose uptake, more in the fed state. So do you have any data as far as, you know, glucose-stimulated insulin responsiveness in any of these kids?

DR. QUIGLEY: We do have some post-prandial insulin data--again, from the old Turner's syndrome studies.

DR. TAMBORLANE: But not in the--

DR. QUIGLEY: Not in this--no, not in this

patient population.

DR. TAMBORLANE: Now, the other thing that--I'm almost certain that the .375 is going to affect insulin responsiveness, and probably insulin levels. That, of itself, may not be bad, because I think that actually may be part of the metabolic cascade that drives the improvement in growth.

The things you worry about are subtle effect of hyperinsulinemia on other systems. As far as I can see, from the safety data, there was only, you know, one child who develop hypertension. But do you have more complete analysis, looking at changes in, say, blood pressure SDS scores in these kids over time? Because we know that changes. Do you have any data as far as lipid profiles, or other--you know, potentially concerning changes as you go up on growth hormone doses?

DR. QUIGLEY: We have--that patient with--quote--"hypertension" actually had an elevated blood pressure at five weeks on study, which completed resolved thereafter spontaneously. So probably, in fact, did not have hypertension.

I don't believe we have any--we did not see any outstanding changes in blood pressure across the durations of the study. I don't think

we expressed them as standard deviation scores, but in the age range that they were in, they may not change markedly across that time period.

DR. TAMBORLANE: A normal child will have an increase in blood pressure over time.

DR. QUIGLEY: Right.

DR. TAMBORLANE: So if you didn't see a change in blood pressure--

DR. QUIGLEY: What I mean--

DR. TAMBORLANE: --I'm questioning--who was measuring the blood pressure? Not that--you know, to not see an effect.

DR. QUIGLEY: I may not have been clear. I didn't say we didn't see a change. I meant we did not see a change between the groups across the duration.

DR. BRAUNSTEIN: Dr. Schade?

DR. SCHADE: I have a couple of metabolic questions.

Nobody seemed to address the mechanism of the growth. Does Lilly think that that's due to the normalization of the small increase in IGF-1 that occurs?

The reason I'm asking this question is that I gathered from the data you presented that

not everybody responded. And my question--if that's true--my question is what are the guidelines for physicians as to when to stop therapy. This is a very expensive therapy, and it occurs over years. I mean, the data you just showed, over five years. And if there are non-responders, what are guidelines or mechanistic ways that we know to say, well, this child is not going to respond to this treatment. We don't know why--obviously, we don't know why this child has short stature to begin with, because theoretically, the child has been worked up for known causes of short stature.

My question is what can we tell the physician about when we know this therapy, after a year or two, is not going to suddenly add another one or two inches of growth?

DR. CUTLER: Well, I certainly agree there's variability of response, but it's not clear that the higher dose that we looked at in the dose-response study that there were non-responders. All of those patients--or 94 percent of the patients made it into the normal range, and the one who didn't had a very appreciable increase in the height SDS of 0.9 over the course of the study.

The mean gain in standard deviation score

was 1.85 for that group, which is well above--way above anything that could be expected spontaneously.

So, I'm not confident that there are non-responders. I think that, in terms of the variability of response, we really don't have a validated way today to pick the very good responders, who are going to have more than a four-inch gain over the baseline predicted height, from the patients who are going to have a two-inch gain.

And that, I think, is something that's of interest to us, that we're looking at, as are others. It's part of our GeNeSIS program to have a growth-prediction module, which we're inviting patients to take part in, where we're collecting a number of parameters and looking at improving short-term and long-term prediction.

But, at this point, we really don't have a way to predict the variability of response in advance.

DR. SCHADE: Okay. Well, let me ask you a little more specifically--I hear you saying there's no correlation, then, between the change in IGF-1 or the levels of growth hormone that might be achieved. I realize you're using different

dosages, but if you actually look at the growth hormone levels achieved, there is no correlation between the response and the change in IGF-1 or growth hormone levels achieved--not the dose.

DR. CUTLER: Mm-hmm. There's very poor correlation between the changes in IGF-1 and the changes in growth. I wouldn't say there's no correlation, but way below what could be useful for clinical prediction. And this has been found in all of the indications, actually, even in growth hormone deficiency where you would think, if anything, it would be strong. It just has not proved to be a reliable predictor.

DR. SCHADE: Okay. Well, let me ask you one further question--just to help the physician.

If you treat the child for a year, and you get a certain degree of response, either the rate of increase--whatever--can the physician use that data, then, to predict what will happen over the next four years? Or the subsequent four years?

DR. CUTLER: Just let me be sure I understood the question that I was also thinking that Charmian--

DR. SCHADE: Well, I'm asking about--

DR. CUTLER: The short term response and

long term?

DR. SCHADE: I'm asking about poor responders--

DR. CUTLER: right.

DR. SCHADE: And what the physician can tell the mother or father about what will happen subsequently. Because somebody is paying $20,000, or whatever the cost is, per year--

DR. CUTLER: Right.

DR. SCHADE: --and does the first year response automatically predict the subsequent four years' response?

DR. CUTLER: Right.

DR. SCHADE: That type of information, I think, the physician needs--

DR. CUTLER: Right.

DR. SCHADE: --because a mother's going to come in and say, "Well, my child hardly grew this year." What will I know about the subsequent four years?

DR. CUTLER: Right. The simple answer is that there is some predictive value of the early--or there may be, let me say. It hasn't been excluded. But from our data, very, very weak. We've done this for six months' height velocity,

and the correlation coefficient was .07. So almost zero.

And one of the reasons you can imagine that might be the case as we study a peri-pubertal group, where some of the children might be beginning to enter puberty, and having growth spurts that were puberty-related, it has not been very useful. However, it is not an uncommon practice, if you give growth hormone and there really is no increase in growth velocity--which is pretty uncommon at a higher dose, but could occur at a lower dose--either to increase the dose--and some practitioners will take this approach--or to discontinue therapy, if you're at the highest dose you're comfortable using.

DR. BRAUNSTEIN: I have a few questions, also.

We had requested the actual final height data from the pivotal study. And in calculating the difference there was actually--it worked out to about 2.8 centimeters. Yet your slides, using the SDS and then converting it to centimeters was 3.7 centimeters.

I know that that could be a statistical quirk, but the actual height difference only

appears to be 2.8 centimeters in total, which is less than an inch-and-a-half.

DR. CUTLER: This is the difference in final height minus baseline predicted height--

DR. BRAUNSTEIN: Yes.

DR. CUTLER: --for the two groups? Right.

And you know, if you look at the extended tables--and that analysis is correct. And actually it's also shown on one of the later slides.

I think what we can say is there are a range of efficacy estimates in the package. And we've given all of them to you. They range from a low of about 2.4 to a high of about 6.7, and I think there are 30 different efficacy estimates in the briefing document. The median of them happens to fall right on the primary analysis of 3.7.

And I think what you have to realize is they're each different methods. They each have their strengths and weaknesses. Height prediction has variability and error, and it could go one way or another.

So I'm not convinced that that analysis is lower because it would always turn out that way, as much as that's just what happens if you do a number of analyses, you'll find different results.

DR. BRAUNSTEIN: But that's what the data showed.

DR. CUTLER: Yes.

DR. BRAUNSTEIN: I mean, you had the height prediction to begin with, and then you had the actual measurements afterwards.

DR. WATTS: Are you looking at this--

DR. BRAUNSTEIN: Yes.

DR. WATTS: That's in inches, not centimeters.

DR. BRAUNSTEIN: Yes--I converted it to centimeters, though. Because they're using centimeters.

DR. WATTS: It's two inches, so it would be 4.6 centimeters.

DR. BRAUNSTEIN: No, no, no. I'm sorry. I didn't mean inches. I meant 2.8 centimeters. It works out to 2.8 centimeters when we do the conversion.

DR. CUTLER: Maybe you could--

DR. BRAUNSTEIN: It was a little over 1.1 inches.

DR. CUTLER: --show me which figure, or table--which analysis you're looking at, just so I'll--

DR. BRAUNSTEIN: This is the--we had requested the actual data on the 11 control patients and the 22 Humatrope-treated patients--

DR. CUTLER: Right.

DR. BRAUNSTEIN: --looking at the predicted height and the final height, and the difference. And when you add that up, if you do it in inches, the Humatrope-treated patients gained a mean of .84 inches, and the placebo patients lost a mean of .274 inches. So when you add that together, you get a little over 1.1 inches difference between the placebo group and the Humatrope-treated group, which is less than 3.7 centimeters difference.

DR. CUTLER: Right. Right.

DR. BRAUNSTEIN: And so what I'm saying is--

DR. CUTLER: Can I explain the difference?

Let me tell you how the 3.7 centimeters--let me tell you how the two were calculated, and I think you'll understand. I hope you'll be able to explain why they're different.

The 3.7 comes from an analysis of covariance. And basically in that data you plot, you know, all of the final heights versus baseline predicted, very much like one of the core slides,

with that diagonal there. And then the model simply does a least-squares mean through the two populations and tells you that the mean difference, making the slopes for those lines being the same, is 3.7. So it is attempting to correct for baseline predicted height.

You will not get the same answer if you take each individual patient and then subtract their individual baseline prediction and average it, as you do if you get a least-squares mean.

Now, the statisticians for some reason feel that the ANCOVA model, where you basically have a regression line through the green points, a regression line through the pink points that's forced to have the same slope and you take the difference, that difference corresponds to 3.7 centimeters. That is not the same as taking this, plus this, plus this, plus this, plus this and averaging them. And--they just come out different. I mean they're two statistical approaches to look at a similar thing, and they don't come out the same. But there is no intrinsic reason to believe that that averaged approach is more valid. In fact, I think the statisticians feel that the least-squares mean is likely to be a more

appropriate analysis.

And I probably said more statistics than I should already.

DR. BRAUNSTEIN: Let me ask one more question.

It seems to me that there's two problems that you want to correct with the short kids. One is you want to correct the childhood shortness, and have them come closer to their peers--their taller peers, and the second is you want them to turn out to be normal sized adults. So those are the two issues.

As far as--and a lot of the arguments that you use concern what happens to short adults as far as their ability to manage their environment, and how they're perceived and things like that.

Taking that into consideration, why not use a predicted height less than 2.25 standard deviations below the mean, rather than taking the actual height at the time the child presents, since we do know that many of these children have a delayed bone age, and therefor their predicted height will be greater than the minus-SDS that they're presenting with?

DR. CUTLER: I think the key reason is

that most of the pediatric endocrine community recognize that predicted height is a useful research tool, it's also a useful clinical tool as an aid to judgment, but it's, in the real world, fairly imprecise in its application. It often depends on the radiologist's reading of a bone age or, even if it's individual physicians reading the bone age, it's a fairly imprecise element.

I think that all of the people that we've talked to in the pediatric endocrine community feel it would be much better to stick with a real measured height, and a real measured height SDS than to introduce that variability.

And I might--I think I'd like to get one of our--maybe Dr. Rosenfeld, if you'd like to comment on some of our consultants who are really doing this every day.

DR. ROSENFELD: Well, I think the--my name's Ron Rosenfeld from the Packard Foundation and Stanford University.

I think Dr. Braunstein's question is one that, in fact, we debated quite considerably with the people from Lilly. I think you are right in saying that there are some children, because of delayed puberty, who may catch up. But you have to

put into perspective the kinds of children we're talking about here.

As Dr. Cutler showed you these children, on average, are coming in minus-2.8, minus-2.9 standard deviation. Very few of those children are likely to enter into the normal growth curve anytime during childhood or adolescence. Very few are likely to achieve a normal adult height. And the experience of the pediatric endocrine community has been that evaluation of skeletal age simply has not proven to be an effective way of predicting which children are likely to enter into the normal adult range.

Given the inability to predict effectively, and given the fact that these children are so dramatically short when they present to a pediatric endocrinologists, it was our feeling that we could not discriminate between the group that would catch up and those that wouldn't, and that our recommendation would be that all at least have access to growth hormone therapy.

The point was made earlier that there appeared to be, on some of the slides from Lilly, a small catch-up period that accumulated over time. In fact I believe you raised that point.

In fact if you look at that slide, what we're talking about is an average of a .1 standard deviation per year in this spontaneous growth. That's a remarkably small spontaneous catch-up. These children come in, on average, at age seven, minus-2.9 standard deviations; they're going to come back at age eight at minus-2.8 standard deviations; at age nine, minus-2.8 or minus-2.7 standard deviations. It's very difficult for us to withhold the availability of growth hormone to such patients, when at the same time we're treating other patients with the same degree of short stature.

DR. BRAUNSTEIN: I think what we'll do is we'll give Lilly a break for a little while, take the next presentation and then some questions on the presentation and break for lunch. And then we'll have ample opportunity to continue the questions after lunch.

So--thank you.

Yes?

[Voice off mike.]

DR. BRAUNSTEIN: One more minor statistical question. Dr. Grady.

DR. GRADY: You know, I'm trying to figure

out the different--there was different--I think you reported, although it was hard to figure out which population you were talking about--a different duration of follow-up. And it looked like it was as much as half a year longer in the treated group than in the placebo group.

And I can't quite figure out how that affects your efficacy estimates. I mean, if it's ANCOVA that we're looking at, then that could be an issue. Could you discuss that?

DR. CUTLER: You're talking about the pivotal study and the final height. And actually the final height was measured six months later in the placebo group than in the Humatrope group, although it was not--that was not a statistically significant difference. The placebo group at 19.1, and the growth hormone-treated at 18.6.

And I think the longer duration of growth in the placebo group might account for that very small difference in the FDA briefing document, where they did the whole analysis in actual final height centimeters and came up with 3.2, whereas if you do it in height SDS--which really corrects for a single age--the way that's traditionally done is you take the SDS at the end, and then in converting

to centimeter estimates you convert it to height SDS at 18 years, in order to try to remove that age imbalance. That's sort of the way it's done when you--traditionally when you convert these difference to the centimeter equivalent.

So it essentially the way that we have done it removes the age imbalance, and I don't think it's a significant issue.

DR. BRAUNSTEIN: Okay. Thank you.

The FDA has invited Dr. Harvey Guyda to make a presentation. He's professor of the Department of Pediatrics at McGill University, and has extensive experience in this field and has written extensively about it.

Presentation

DR. GUYDA: Good morning. I guess it's almost good afternoon. Thank you to the committee for inviting me.

To give you just a bit about my credentials, I've been in the fraternity of pediatric endocrinology for 37 years. It seems longer than that some days. I also have to add another disclaimer to what Dornette has given you: I am from Canada but I do not come from Toronto.

My task--and I've allotted myself only 20

minutes--is to focus on three areas. And the first is some comments regarding efficacy for final height; some comments regarding cost-benefit analysis; and some comments related to ethics, particularly psycho-social enhancement. And I am not going to talk about social policy, equity, fairness and resource allocation. That's been partly covered in a few words this morning already, but also is covered in some of the reference materials that's been provided, and quite a bit in the literature.

So, definition of "short stature"--you've heard quite a bit of what's normal, so I thought I'd just review that, from my perspective, very quickly. And this actually comes from a consensus statement that was published in 1996, following a meting of my esteemed colleagues.

The first--and the one I want to remark on most--is the "normal size at birth"--and of course this was violated by both studies, the E001 and the trial from the NIH; significant short stature is, you've heard generally, minus-2 standard deviations. And we've heard the problems of SDS and how it varies over time.

The issue of tempo of growth during

childhood is one that has been either taken into full account or disregarded. I personally think it's an important aspect in assessing a child with growth failure, but this was not put into the consensus statement, and was not a parameter in the randomized controlled study at the NIH, but was a parameter in the European controlled trial.

And, of course "no evidence of systemic disease"--this was also violated in at least one of the patients in the controlled trial, had hypothyroidism on T-4 treatment.

So what's "normal?" I thought I'd just spend a few minutes for those who are not pediatric endocrinologists. You've heard about disease scores, or STD scores--they're on your left. The percentiles are on the far right. And I've just listed some numbers so that you can put this in perspective of what kind of numbers we're talking about.

You heard the definition that I gave you on a previous slide of minus-2 standard deviations. That's actually 2.3 percentile, and these are the actual figures in centimeters. You can see they're very close to these two numbers over here. So, about 59 inches, and just a little over 63 inches

in your terminology.

The criteria being proposed today are the 1.2 percentile. That's equivalent to 5'3, and about 58-1/2 inches. And note that the minus-2.5, which is a 0.6 percentile is 58 and 62 inches respectively. Note, however, that even if you're able to move someone from this percentile over here, or this SDS score, they're still going to be a considerable way from the 50th percentile, which is listed at the very bottom of your slide for reference.

This is some earlier data I published in 1999, before I reviewed some of the current data that's been presented this morning. This was the consequence of an international survey--again, uncontrolled data, but it's remarkable how it came very close to the overall bottom line, which is a change in centimeters of 2.7 centimeters, and a change in SDS of 0.4--not unlike what we've just heard attributed to growth hormone this morning.

This is also a study that is a little bit of an outlier that Ray Hintz has published, and the reason for the slight improved benefit, in terms of 5.5 centimeters, 4.9 centimeters remain unexplained, expect perhaps younger age and less

advancement in bone age. Correct?

[Comment off mike.]

DR. GUYDA: Higher dose.

Now, this has been common--and there was a question from the panel, statements just recently from Dr. Rosenfeld, and I beg to differ. Short kids do catch up. And this is a total of almost 500 children. This is their initial height at assessment. This is their final adult height. These are measured, these are not predicted adult heights. And you can see that the average at baseline, when they were first observed was 2.2 SDS, and they gained as a group, collectively, 1.2--this is greater than your Humatrope effect that's been reported this morning. And the same for females, identically. And this is a very large study. It's larger than both of the studies combined, in terms of final height.

So if I make some comments on the GDCH study, this is my particular interpretation. Height velocity was only calculated before randomization for six months. It's well known that transient growth deceleration can be a severe phenomenon in a few kids--not all kids, but some kids--and then over a subsequent six months over

observation they can show a catch up. In one study we reported there was doubling of the growth velocity. So measuring children and enrolling them in a study after only six months of observation I do not think is a wise choice.

As I said earlier, it included small-for-gestational-age children. These, by definition are not idiopathic short stature. They have pre-natal onset of growth failure of undetermined origin.

Also, there was an inclusion, to get enough patients in the study, up to a bone-age of 13 in boys, 11 in girls, and the complicating factor of trying to assess growth change in children undergoing puberty of course became paramount because a significant number were already in puberty when they began the growth hormone treatment. And I made reference to the hypothyroidism issue.

You've just heard, and it's been acknowledged, that the dose was on the low side. Particularly for those children who have normal growth hormone secretion the current data is that you need to give more growth hormone if you're expecting to see some benefit. And, again, the issue of only three times a week--this was actually

discussed in the minutes of the FDA meeting in 1987. It was pointed out even then that three times a week was not as good as daily or six times a week.

What concerns me particularly is the high dropout rate. Only 16 patients were left in the growth hormone arm, and 9 in the placebo, leading to only 42 percent of the original cohort for growth hormone, and 27 percent placebo. That suggests that there could be a positive bias of those who, in fact, remain in a treatment arm.

The overall treatment effect, in my opinion, was quite modest. The gain we've heard and were discussing whether it's really 3.7 or 2.8 or 9--it's in the range of a half SDS. Again, that will depend on how you convert that. But take a look at what this would actually do. If, in fact, the entrance criteria is minus-2.2 SDS, and you're successfully able to add a half an SDS to that child, it gets them up to the 3rd percentile, however, he'd still be 12 centimeters below the mean. So then it becomes a moot question: what's normal? Are you normal when you're at the mean? Are you normal at the 5th or 10th percentile, or are you still normal when you're at the 3d percentile?

Up until this morning we did not have access to the psychological data. And, as you've heard, it would appear that the data is inconsequential.

These are re-analysis from the statistical consultant to this committee. So there are two figures coming up. On the left-hand side is the no-final-height grouping, and those on the right are the final-height patients. Again, look at the numbers. The Humatrope, in the females, there were only four; there were 18 males. And there are the placebo in pink. And what we're arguing--or discussing, I guess is a fairer word--is this benefit up here for these four or five patients. There are the placebo, and there are the growth hormone treatment. And there's even a bigger scatter in this group over here.

So, visually, the dots do not suggest a huge impact on many children and, in fact, they were no different than the placebo group.

This is just segregating them by where they're coming from, in terms of predicted height of less than 5'6" or more than 5'6". And, again, the data are similar. There's some modest benefit shown with Humatrope, but it's not an overwhelming

visual impact when you look at the data points.

In terms of the E001 study, there was a dose effect, as indicated here on the slide, and which you heard reference to. Again, significant numbers, when you look at the raw data points, overlap with the placebo group of the GDCH study.

Again, a very high dropout rate--almost 13 percent during the first two-year evaluation period, and there were actually only 50, representing 21 percent of the original randomized subjects in the final-height cohort, and half of these were seen in one center only--22 patients in one center. It was a Dutch center, and one might suggest there may be some genetic influence on that particular population for example.

Interestingly, the highest dropout rate--38 or 46 percent--was in the high-dose group. And that was particular to me if, in fact, that group was showing the highest benefit, why that group would have the highest dropout rate.

In trying to analyze the meta analysis, which is an interesting feat sometimes, I actually asked a consultant who works with me in my department--she's a pediatric editor of the Cochrane Reviews--she assessed the merit of this

meta analysis at level two. For those of you not familiar with this scoring, a level one is a top-graded meta analysis, a level three is not worth really spending too much time on, and this is level two--in between. And it was rated this way because of the fact that it was a mixture of controlled, uncontrolled data, non-randomized, and very small numbers in many of the studies. And so this could lead to a likely bias for positivity.

As you heard earlier this morning, there were only four controlled studies to adult height; 84 on Humatrope, and 104 controlled. There were multiple dropouts during the group ending up in adult height. Again, observed was similar to what you've heard earlier; a gain of half a standard deviation score, in the range of 3 to 4.6 centimeters over predicted, and over the control group, .84 and 5 to 6 centimeters. It is likely if these were randomized controlled studies, the smaller effect would be seen.

Again, the parameters were different from the randomized controlled study at the NIH. Less than 10 percentile was used--and we haven't heard much discussion about whether that really is abnormal, and why those patients were getting

growth hormone treatment. We've heard that minus-2 standard deviations is the benchmark. And, again, SGAs were included.

Some cost factors--this is something published by Bailey in 1992. I guess you can multiply up the numbers, since things have escalated. And the estimate at that time, if you were to treat the lowest 1 percent of the population in the United States, you would spend approximately 3 billion. Estimates in our materials provided to us were in the range of 10 to 20 billion, potentially. And, again, you have to look at the poor lowly NIH--although it has had a recent burst.

This is an interesting study, and I recommend this for those who haven't come across it yet. This came out of Brant in the U.K., and it's a very large analysis of cost-effectiveness of various treatments in different categories. So I've listed, for a reference, what the normal range is; untreated adult height, the growth hormone dose, the growth hormone adult height estimated mean, and the cost, that I've converted into U.S. dollars from the British pound--cost per centimeter.

And, again, the growth hormone deficient is the most efficient, if you will, and achieved relatively good adult heights for the lowest cost-per-centimeter, roughly 10K. Chronic renal failure, quite variable, depending on what age you're treating, so the size of the patient. And, again, achieving low normal heights but, $10,000 to $40,000 per centimeter. And this is per centimeter.

Here's the group for idiopathic short stature. And, again, the doses are in this range. Predictions are potentially that mean adult height, and the doses are up, again, as high as 40-odd thousand dollars per centimeter. So, times three centimeters, that would be about $120,000, roughly. And then Turner's, for reference, is at the bottom here, again with the highest dose that's been approved so far, costing roughly $25,000 to $30,000 per centimeter.

So these are very expensive centimeters.

The other issue is: is this really a medical problem or a social problem, or whose problem is it? Short stature is not a medical diagnosis, as you've heard. It's really a descriptive term for a person whose height is

considered to be significantly below some arbitrary normal range for that age, gender, racial group and family structure.

It's also a statistical term, and that's what we've focused on mostly this morning. It's generally referring to people who are shorter than the 97th percentile of their age and sex-matched peers. Thus, in any population, nearly three out of a hundred would meet this definition and be called short stature, even though they have no medical abnormality.

And, as we all know, height perception is influenced by a wide variety of factors, including culture, gender, family background and psychological state.

I'd like to address the psychological state issue, briefly. These are just some of the references that have been published on this topic. Basically, dating back almost 10 years--and this was made reference to earlier this morning--if you look at short stature in a population-based group and not in a clinic-referred population, there is not a clinically significant psycho-social morbidity. Several studies from Gilmore and Skuse in the U.K.--little evidence to suggest that even

in a clinic-referred population, untreated short stature children are psychologically maladjusted.

And then Downie--there was actually a study involving growth hormone treatment and not-growth hormone treatment, and there was no psychological benefit of growth hormone treatment in that particular study.

And then, finally, looking at adults who were short stature in childhood, and evaluating them as adults, they did not show any psycho-social distress or impairment, and therefore did not provide evidence for growth hormone treatment of short stature in childhood.

I'd like to just refer you to equipoise, and how this could be applied to this discussion. Equipoise demands that the following three psychological effects are considered before assigning benefit in short children treated with growth hormone. The first that, indeed, it's beneficial, improved self-esteem due to increased height velocity or increased final adult height; it's harmful, due to disappointment with final adult height or poor self-esteem due to increased medicalization, daily injections and other issues related to non-improvement; and then neutral, no

psychological benefit. And that's, I think, what we heard from the randomized trial this morning.

So, in summary, the number of subjects in randomized controlled studies of growth hormone therapy to final height is very limited, and this includes the small numbers in GDCH.

The final--again, just to repeat, as you've heard many times--and the real question we're debating--is this clinically significant, considering that there was quite an overlap with the placebo group who showed spontaneous catch up? A majority of studies are uncontrolled, and final adult height attainment over predicted adult height--which we've heard the problems of predicted adult height--has indeed averaged less than one standard deviation, and this is presented to you, identical what has been published in almost 500 children with spontaneous height gain in children who were called idiopathic short stature.

An interesting study, again, from Ranke: in 236 normal short children, two-thirds spontaneously achieved normal adult height. One quarter did not, and only 10 percent did not reach the familial target height. So the outcome for this logged cohort was actually quite positive.

Few studies have actually addressed the downside or negative outcome. You can infer this, maybe, from dropouts. In Australia, in a study in 1996, out of almost 1,400 children who were receiving growth hormone for idiopathic short stature, one-third did not complete the three years of treatment. And this is, as in the studies reported this morning, due to patient decisions in the large main. In the particular GDCH study reported this morning, only 28 of the placebo and 42 percent of the growth hormone therapy group actually completed the study.

And as I've indicated, few studies have addressed the psychological benefit of growth treatment to final height for idiopathic short stature, and this continues to remain unproven.

Thank you. This is the reference, for those who would like to have the full reference.

DR. BRAUNSTEIN: Thank you.

Committee Discussion

DR. BRAUNSTEIN: We'll take some questions for Dr. Guyda's presentation.

Dr. Gelato?

DR. GELATO: Maybe I'll just bring this up now, and sort of get people's feel about it.

In August of 2002, the Lawson Wilkins Society gave recommendations for giving children who have short stature a trial of growth hormone if they met certain criteria. And I just wondered what people thought about the Lawson Wilkins proposal, which listed several things: a height more than three standard deviations below the mean age, or two standard deviations below mid-parental height centile; a growth velocity less than 25th percentile for bone-age; a bone-age that was delayed by more than two standard deviations below the mean; and then a low serum IGF-1 and/or IGF-BP3, or other clinical features of growth hormone deficiency.

And their feeling was that if children met most of these criteria, it would make sense to give them a trial of growth hormone. And I just wonder what people thought, because this seems to be different than what we've been talking about. Obviously these are children who are more severely affected, but still was the recommendations of one of the pediatric societies. And I just, you know, throw it out for a point of discussion in terms of everything that we've been talking about, and what people feel about it.

DR. BRAUNSTEIN: Harvey, you want to comment?

DR. GUYDA: Hah--is that question for me?

DR. GELATO: Well, I just--I'm just curious, because, you know, they've given guidelines, and yet it seems like there's--

DR. GUYDA: I actually would like to comment on guidelines, because earlier we heard this morning that the pediatric endocrine fraternity, to which I belong, are efficient gatekeepers. If you look at the databases-- and you saw presented by Dr. Quigley this morning--there's almost 6,000 short children in NCGS, and almost 4,000 in KIGS who are getting growth hormone treatment--off-label use; gatekeepers giving it to all those children. That represents about 25 percent of NCGS.

So, gate-keeping and making recommendations don't seem to translate into what happens out in the field. And if you recall the last published statement of the Lawson Wilkins was that growth hormone should not be used for non-growth hormone deficient short children, and this has not prevented this--it's over 10,000 children in the U.S. getting growth hormone for short

stature.

DR. BRAUNSTEIN: Dr. Cara?

DR. GUYDA: I agree the more rigid you are and more strict you are, you might identify those children who are going to have potentially a better benefit. And I think the target for all of us in pediatric endocrinology is: how to dice up those kids? How do you find the ones who are going to be above the placebo, and the ones who are going to benefit? And we haven't gotten there.

And I know Ron, and Ray and others have tried very hard to look at short-term and long-term predictive--both biochemical and oxyological data. It just hasn't worked in large groups. Individually sometimes it works, but in large groups it hasn't been very useful.

DR. BRAUNSTEIN: Dr. Cutler, you want any of your consultants to also comment on the question?

Dr. Hintz?

DR. HINTZ: Dr. Hintz, from Stanford. Just a quick comment on the implication that that was an official statement from the whole Lawson Wilkins Society. That was, you know, three people from the Drug and Therapeutics Committee writing and article

with some proposed criteria.

So--and I personally felt at the time that those were extremely conservative criteria. In fact, if you fit all those, you've got growth hormone deficiency.

DR. BRAUNSTEIN: Thank you.

Dr. Cara?

DR. CARA: Harvey, could you comment on the sort of observed efficacy of growth hormone as a function of time? Specifically during the pubertal years, and perhaps related to a graph that the FDA presented on page 27 of their briefing document--of their review--looking at 12-month height velocity, versus years of study.

I don't know if you saw that?

DR. GUYDA: Actually, I'm thinking more of what the statistical consultant did with that kind of data. It was clear that some children actually accelerated and gained in their SDS, but when you follow them to the end, they actually ended up not quite as high as they had been.

So--the numbers are small. And we've heard that bone-age in puberty were not different, but the numbers are too small to really indicate whether, in fact, that particular subset of

patients did have an earlier puberty, an earlier acceleration and ended their growth earlier, and then started to fall off.

DR. BRAUNSTEIN: Yes--Dr. Grady?

DR. GRADY: I just wanted to ask for your opinion. You know, again, we're talking about here perhaps making eligible one in every hundred children for treatment with a hormone at--early in life, for multiple years. And we haven't spent much of any time on the potential adverse effects.

Clearly, the studies have been too small to give us much information on death or serious adverse events. But, I mean, are we--is this assumed by most pediatric endocrinologists to be a safe therapy?

DR. GUYDA: Ahh--well, actually, I was going to ask the question, but I realized it was committee-only asking questions earlier.

When Dr. Quigley was presenting the safety data, and was using the reference as indicated use currently, it was curious to me that the recent sudden publication of seven deaths in Prader-Willi were not mentioned. So there are surprises out there. Whether that's directly related to growth hormone or not is still a moot point. We'll have

to wait over time and see.

I can't use the CJD model, because that was pituitary extracted, obviously; the leukemia model caused a big flurry, but over time that seemed to settle down and did not seem to be statistically more increased.

I think one of the concerns--two areas of concern bother me. Dr. Tamborlane made reference to the possibility of the insulin glucose issue and prolonged hyperinsulinemia over time, and what that might do over time. And the other issue--are the values of IGF-1 really--particularly if we're going to go up to .375 or higher--are they going to be above normal, and what is that impact going to be on tissues who are both sensitive during pubertal growth spurts, but ultimately down the road, in terms of neoplasia.

And I think that remains a big concern for me, even though there's no data to support the fact that that's going to happen, we can anticipate there may be something along that line, but we don't have the data on that.

DR. BRAUNSTEIN: Other questions from the committee?

DR. FOLLMAN: Yes, I have one.

Slide 5 you showed the spontaneous adult height in children with short stature, and you showed some very large increases--like on the order of greater than one standard deviation score.

Could you go into a little more detail about that data?

DR. GUYDA: This is--

[Pause.]

--sorry. Not my computer. Find the mouse here. Here we go. Aw, this is going to take forever.

[Pause.]

DR. BRAUNSTEIN: Yes, this is the slide.

DR. GUYDA: This is just published literature again. It's measured height, not predicted; and Ranke particularly is someone who is very interested in the whole issue of short stature.

The other issue that we didn't touch on too much, and I didn't stress in my publication, in both the randomized study, controlled study, at the NIH and in the European study, there's about a two-year delay in bone age--as a pediatric endocrinologists in my clinic, when I was taught by Robert Blizzard, if you had more than one standard

deviation delay in bone age, that then had to raise the concern of whether you had a chance for a delay in puberty and a different prognosis than someone who only has--quote--a "normal" bone age within, say, one standard deviation.

So there is a delayed bone-age effect, and a good part of this data would be probably related to kids who have a delayed bone age and get to be--I think you asked the earlier question--if you're starting at minus-2 standard deviations, and then you have a delayed bone age, you're going to probably get to be taller than that eventually.

And I think this is partly what this data reflects. It's very hard to distinguish kids who are absolutely just normal short stature, and those who have some delay in bone age, some potential for delay in puberty.

Does that answer your question? I'm not sure--

DR. FOLLMAN: Well, I had a question--that partially answers it. I was curious about how these patient were selected. Were these just all observational studies of short stature children that they got at the clinic? Or--

DR. GUYDA: No, these are pediatric

endocrine clinics. It's the single most common cause of referral to a pediatric endocrine clinic, so you can run up these numbers pretty quickly.

DR. FOLLMAN: Thank you.

DR. BRAUNSTEIN: Yes--Dr. Woolf?

DR. WOOLF: Getting back to the--let's say the non-orthodox use of growth hormone in short stature, and your allusion to gatekeepers, how do those people--how did these kids in the States, do you think, got treated if, in fact, all these checks and balances are in place to prevent that?

DR. GUYDA: I really think that should come from the providers of growth hormone.

DR. BRAUNSTEIN: And we can ask that question after lunch.

A few others?

DR. MacGILLIVRAY: It's important to remember that the children we're talking about are as short as the children with growth hormone deficiency, but test out with a peak growth hormone above 10 nanogram per mil. And the insurance companies approve growth hormone for growth hormone deficiency based on the stimulation tests. So the children who are currently receiving growth hormone from--for idiopathic growth failure or short

stature, or non-growth hormone deficient growth failure are children who have pathologic height and often pathologic growth rate, and when they're followed over time, their height is progressively falling further away from the 3rd centile.

When you apply to the insurance companies, you will get rejected. And then the next thing is you make an application for some of the foundations run by certain pharmaceutical companies to assist you with a six-month treatment trial. If in that six-month treatment trial you show a significant improvement in growth rate--by that I mean a growth rate annualized of 9 to 12 centimeters a year, you go back to the insurance companies and say to them: it is possible that that child's able to respond to stimulation tests, but they're pituitaries may be under-producing growth hormone because of insufficient GHRA, or that the potency of the growth hormone they produce is sub-optimal, but they are responding to growth hormone.

So it's extremely important to look at responsive children, and then you make the decision to keep going every six months. So a majority of these children are receiving growth hormone because they are responders in the first six months.

DR. BRAUNSTEIN: Dr. Grumbach, do you want to comment?

DR. GRUMBACH: I think that Harvey has pointed out something important, but I'd like to criticize some of the data on that slide.

For example, the Crowne studies from Manchester--and their study was looking at kids with very marked constitutional delay in adolescence. Now, they got to 1.8, but that was less than their--what you would get from family height. In other words, their--based on mid-parental height, they were still below what they should have achieved.

That's also true of the LaFranke study, which was from Portland--both of these are really very nice studies--again delayed adolescence. They got to 1.2, but that was about a mean of over a centimeter less than their mid-parental height; what their predicted height was.

So I think what Harvey has up there are a lot of kids that we all see, with severe constitutional delay; very marked delay in bone age, and we're all aware that many of these catch up.

But the important point that's come out of

these long-term studies--that they don't catch up to their predicted height; to what their--based on mid-parental height. They all end up, as a group, lower.

DR. BRAUNSTEIN: Thank you.

Dr. Rosenfeld?

DR. ROSENFELD: I'm a little bit concerned that Drs. Cutler and Quigley are somewhat constrained in their presentation by feeling a need to adhere strictly to the data from the Lilly studies. And I"d like to just take a minute and put it in a broader context.

First of all, I was quite struck by their data, in that it is, for better or worse, the one and only placebo-controlled trial to adult height and will never be duplicated. Even given the fact that, as Dr. Guyda pointed out, they used initially sub-optimal dosages, sub-optimal regimen, in terms of three times per week, and an older age group than one would ideally choose if one were doing this study now, they still showed a statistically significant effect, no matter what statistical parameters were employed.

Secondly, in their dose-response study, they corroborated their ability to show a

statistically significant effect, and a dose-response.

I think, given that context, and given everything that we've seen over the last 20 years, in terms of growth hormone administration, I think that perhaps those of us who are not so constrained to use the Lilly data would say that this is a highly conservative estimate of what the impact of growth hormone therapy can be in this group of severely affected non-growth hormone deficient short stature children.

The data show that these children do not enter into the normal adult height spontaneously; that there is a dose-response; that, given optimization of regiment and higher dosages, just as has been seen with other applications of growth hormone, as in Turner's syndrome, this is a highly conservative estimate.

So, while I understand that we are limited to some extent by the data that are presented, I don't think we should close our eyes to the fact that these children are severely growth retarded. They are as growth retarded as all of the other FDA approved indications. They do not catch up on their own. And that the data presented are likely

to represent--as the Lilly dose response data have shown--a conservative estimate of the impact of growth hormone therapy in this group.

DR. BRAUNSTEIN: Dr. Guyda, we'll give you the last word before we break for lunch.

Dr. Grady first.

DR. GRADY: Can you just tell me, in the cost-effectiveness analysis that you presented--what was the assumed dose, and what the assumed duration of treatment.

DR. GUYDA: Again, the dosing varied, depending on the indication--whether it was renal failure, or growth hormone deficiency. The lowest doses tend to be for growth hormone deficiency, and the--

DR. GRADY: But for the idiopathic short stature group.

DR. GUYDA: Idiopathic--the range that I presented there was .2 to .4--so in the range that we're discussing this morning, up to .375 in the high-dose study that was reported this morning. So that was the dose range.

DR. GRADY: And for how many years?

DR. GUYDA: Again, most of those treatment effects will vary depending on diagnosis. Chronic

renal failure tend to use it for a period to get them tall enough for transplant, so it's never a final height data particularly. But in the idiopathic short stature group, it's usually in the range of four to five years.

DR. BRAUNSTEIN: Dr. Cutler, did you have a comment?

DR. CUTLER: I just wanted to--I thought I ought to point out just two things about this review that Harvey has shown us.

And one of the things I thought was somewhat deceptive about Dr. Price's review is the title is "Spontaneous Adult Height in Patients with Idiopathic Short Stature." Yet, if you actually read the titles of the papers, all but one of them use "constitutional delay of growth in adolescence." Their--they have selected out that group that we all know catches up because they have the family history of a catch-up, and so forth. It's the group that we all try not to treat.

And one other thing I would say is that of these studies, only one of them has even a mean height that is below the cut-off that we're recommending. All the others have a mean height--this one even has a mean height well into the

normal range. So this is a different population from what we're talking about. We're talking about a much shorter group, and not a group that is specifically being perceived by the authors to have constitutional delay. This is just really echoing the point that Dr. Grumbach made.

DR. BRAUNSTEIN: Thank you.

Dr. Guyda?

DR. GUYDA: I think what we've heard is there are diagnostic dilemmas and there are patient management dilemmas, and there's no easy solution to this.

The issue of what's constitutional delay something we discuss in our clinic and teach to our trainees all the time, in the context of short stature. I would ask Dr. Cutler, who spoke most recently: is a two-year delay in bone-age normal short stature? Or has that got some constitutional delay in it?

Sorry about that.

DR. CUTLER: Yes, I think if we had to settle a definition of constitutional delay we probably would be here all day.

I think there is a criterion--and we could actually show it later, if you all want--that is

published in Williams' textbook. It was the only one we were able to find that could actually be rigorously applied, because it was specific enough. And it's quite lengthy. So it's much more than just--it does have a bone-age delay, but it's not just a bone-age delay. And, certainly, a bone-age delay per se, in my judgment, is not enough--if someone's, you know, minus-3 or 4 SD, with a two-year bone-age delay, that's not enough to say they have constitutional delay in my judgment.

DR. BRAUNSTEIN: Dr. Tamborlane.

DR. TAMBORLANE: But, Gordon, don't you think--I mean, the indication says "height less than 2.24 standard deviation score." So when people are actually applying this, then they're not going to--there's nothing that says anything about without a more than three-year delay in bone-age. So this really opens up treatment for constitutional delay of growth and development.

DR. CUTLER: Well, that certainly would not be our intention. And I think it also would not be the intention of the pediatric endocrinologists because, as you know, we're all trained not to treat constitutional delay. And the issue, I think, that you're raising--

DR. TAMBORLANE: I went to parochial school, and the nuns told me about intentions--good intentions, and where you lead you.

[Laughter.]

DR. CUTLER: Well, I think there will be--this is a good point, and I'm sure there will be time for more discussion about this.

The issue is whether you practice medicine in the label. This is already the only label for any growth hormone indication that has any restriction on even a height cutoff. So this is already the most restrictive. If it should be more restrictive is the kind of debate and discussion you were asked to have.

DR. BRAUNSTEIN: Dr. Guyda? Final comments?

DR. GUYDA: No. I'm done. Thank you.

DR. BRAUNSTEIN: Great. Thank you very much.

We'll break for lunch and reconvene at 1:30. Thank you.

[Whereupon, a luncheon recess was taken to reconvene at 1:30 p.m., this same day.]

AFTERNOON SESSION

DR. BRAUNSTEIN: If we could have the committee take its seats, please.

[Pause.]

Open Public Hearing

Okay. We'll now open the Open Public Hearing. And we'll have read into the record a letter that's been received.

MS. SPELL-LeSANE: Thank you, Dr. Braunstein.

This letter was addressed to the committee from the Short Child Family, regarding FDA Hearing on June 10, 2003.

"We are writing to support the application by Eli Lilly Company for approval to treat non-growth hormone deficient short stature with growth hormone.

"We understand that an FDA hearing is scheduled for June 10, 2003. We would like our letter to be noted and read for that hearing, since we cannot be present in person to testify.

"We want to tell you our story so that the FDA will understand how approval of this new indication will affect our family. My son Bradley is 15 years old, and when he started the growth

hormone therapy he was only 4'10" tall. People still look at him as a young child; child rate at the movies and the theme parks.

"Bradley always looked at himself as a short kid. Now he has grown 2-1/2 inches since January, and now his self-esteem is great. He is always measuring himself to see if he has grown.

"As a parent, I am very glad there is something out there to help my son. Please do not take this away from him. It was not easy to get the insurance company to pay for the growth hormone. We went through a lot just to get started. It just does not seem fair to take it away.

"Again, Bradley has made a significant growth spurt since on growth hormone. We anxiously await the public announcement of your decision on this matter. Respectfully, the Short Child Family, Bobbie, Vicki, Bradley, Amanda and Amber."

DR. BRAUNSTEIN: Okay.

There's also an additional letter in the folder for the committee to read.

Our first public speaker is Patricia Costa from the Human Growth Foundation.

MS. PATRICIA COSTA: Hello everyone. I am

Patricia Costa, the Executive Director of the Human Growth Foundation. I have paid for my own expenses to be here today.

The Human Growth Foundation is located in Glen Head, New York. It is a non-profit organization that has been in existence for over 38 years.

Our mission statement is: "The Human Growth Foundation helps adults and children with disorders related to growth or growth hormone, through education, support, advocacy and research." We receive our funding from our membership dues, the Combined Federal Campaign, United Way, health care providers, pharmaceutical companies, including Eli Lilly, several private foundations, and many individual donors.

On May 9th I read an e-mail from one of our members on our HGF-Peds list. That is one of our internet support groups. In her e-mail, this member stated that her child's pediatric endocrinologist had told her that a new drug application for RGH was being considered for use in children who are not growth hormone deficient. Prior to viewing this communication, I had heard about this through a doctor from Eli Lilly.

I then asked our list administrator to look into this matter further. He found additional information and posted his findings, along with the FDA website, on our list. I then spoke with several of our board members, who felt that it was important for us to have a presence here today, to speak on behalf of the children who would be helped from this application.

When I started to prepare this statement I knew that all the clinical data, studies and testimony of the experts in the field of growth would have been heard and recorded. I am here today to ask all of you not only to consider the medical data that's before you, but also to measure the psycho-social well-being of these children.

Every year we receive hundreds of inquiries from parents who are concerned about their child's height. Inevitably, in every one of these conversations, these parents make reference to their child's low self-esteem. They speak of the teasing, the bullying and the isolation that their child deals with because of their abnormal short stature.

During this initial conversation, we explain the normal protocol that is necessary for

this child to be diagnosed. We send them our educational booklets. These are medical booklets on various disorders that have been written for a non-professional to be able to comprehend. We advise them of our HGF-Peds list, a place where they can communicate with other parents who share the same concerns.

These first communications usually prompt two or three additional calls from these parents. They call not only to inform us of their child's diagnosis, but also to receive the assurance that they will be able to give their child the daily shot, and that quickly this will become a normal pattern in their everyday life.

The next call is a joyous one--the one where the parent informs us that not only has the child grown, but that he or she is happier. One mother told me about the conversation she and her son had after they left the doctor's office after his first three-month visit. Her son told her how happy he was, because some day he was going to be the same size as his friends. The mother then became emotional and said to me, "Patty, I never heard those words 'my friends' come out of my son's mouth."

However, all of our calls do not have such a happy ending. For parents whose children are abnormally short and their problems could not be identified, these parents now have dual concerns: their child's short stature, and their child's self-esteem that is plummeting. We have heard stories of children who have become withdrawn, coming home from school and staying alone in their room; the child who, he himself now might have become the class bully; or another child who is being labeled the class clown. On rare occasions, we hear, as one father informed us, every morning his kitchen has become a battlefield, with his daughter crying and refusing to go to school because everyone laughs at her because she is so tiny.

How can we continue to justify to these children that we know the solution, but because we can't pinpoint the problem, they do not have the right to it? We all know that at some time in every child's life they want to be somebody; they look up to somebody. It might be a movie star, a baseball player, or the President of the United States. And we all recognize this is normal. What also should be normal is for these children to be

able to see eye to eye with everyone else.

You have a recommendation before you, the denial of which will result in a lifetime for these children. These children are our future. Please allow them to grow to their full potential; to grow up to be adults who believe in a system that works and, more importantly, in themselves.

Thank you.

DR. BRAUNSTEIN: Thank you.

Our next speaker is Nicole Costa.

MS. NICOLE COSTA: Good afternoon. I'm Nicole Costa. I live in Glen Head, New York. All of my expenses to be here today were paid for by my parents. They knew that I felt it was important, not only for you to hear my story, but for you to see with your own eyes the results of the application that is before you today.

Before I share my story with you, I would like to thank you for giving me the opportunity to participate in this hearing, and to let you know how lucky I feel to be able to stand in front of you without the aid of a box. This result is due to the wisdom of my endocrinologist.

According to my parents, I had always been on the very bottom of the growth chart. I never

reached the 5th percentile--the magical number that you say is normal--that says you're normal. When I was three years old, my pediatrician told my parents to take me to a pediatric endocrinologist because of my short stature. At that initial appointment, my height and weight were taken; my head, torso and limbs were also measured.

My growth chart from the pediatrician was observed, and my parents' history of their height and development was recorded. We left the doctor's office with prescriptions for several blood tests, a test to karyotype for Turner's syndrome, and an appointment for me to have a growth stimulation test.

Two months later we returned, having completed all the tests. The doctor told us that the tests were all normal. From the test results she could not tell us the reason for my slow growth pattern. The doctor told us to come back in six months so she could monitor my growth.

We continued these six month visits for three-and-a-half years. By then, I was six-and-a-half years old. The doctor, after watching my growth for three-and-a-half years, estimated my adult height would be approximately 4'8". It was

at that moment that my doctor recommended growth hormone therapy, to see if this would change my growth pattern.

After being on growth hormones for three months we returned to the doctor's office. I had grown 3/4 of an inch. On a good year for me, that was the growth for an entire six months.

I continued on growth hormone therapy for almost seven years. It was then that my bones fused together and I reached the height of 5'2". I can't honestly tell you what my life would have been if I was only 4'8", however I do know I would never have been able to go into a department store and buy something off the rack. I would not be able to reach the items on the upper shelves of supermarkets. And, most definitely, I would not be able to drive a normal size car.

What I can share with you are some of the experiences that I went through because of my short stature. I was not able to reach the kindergarten water fountain when I was thirsty. No one on the playground chose me to be on their team because, in their words, "You can't run fast enough because your legs are too short." How lonely I felt sitting on the park bench at the amusement park

waiting for my peers to get off a ride; a ride that I wasn't allowed to go on because I was too small.

When it came time for my first communion, my mother said that it was a special day and it required a special dress. We went to the dressmaker to have it handmade. Neither of us ever mentioned the real reason, which was there wasn't a manufacturer who made a communion dress small enough for me to wear.

In second grade, the teacher required that everyone's feet had to touch the ground when we were seated at our desks. They had to bring in a chair from the kindergarten class for me to meet that requirement. You can imagine how embarrassed I felt.

I always loved sports and wanted to play. However, because of my height I was restricted in my choices.

I began my comments by saying how lucky I was that I was given the opportunity to reach my full growth potential. I hope that by the end of this day, after listening to my story and seeing the positive results of the drug application that is before you, this opportunity will be made available to all the children who now walk in the

shoes I outgrew.

This drug application will make a world of difference to these children. It will make their world a different place.

Thank you.

DR. BRAUNSTEIN: Thank you.

The next speaker is Deno Andrews.

MR. ANDREWS: Thank you.

On my knees, today, I stand two inches taller than the first endocrinologist told my mother that I would ever reach as an adult. However, I was treated successfully with growth hormone, as you guys can see. And I reached a very normal adult final height.

I was lucky. There was a clear diagnosis for me: growth hormone deficiency. My pituitary gland produced no growth hormone whatsoever.

But many children are not as lucky as I was. Their diagnostic tests sometimes suggest that they are not growth hormone deficient.

My name is Deno Andrews. Again, I was successfully treated with growth hormone. And I hope that my story will offer you another perspective to consider before making such an important decision today.

When I turned five, my mother insisted to our pediatrician that something was wrong. Our pediatrician told my mother that I was a late bloomer; that I would catch up; that nothing was wrong--despite the fact that my sister, who was two years younger than I was catching up to me in growth.

By the time I was seven, I was not only the shortest child in the first grade, most kids in kindergarten stood taller than me, including my sister.

As you can imagine, this was a very difficult time for me. On a daily basis I was called words like "midget," "shrimp," "small-fry," "shorty," and a number of other derogatory terms. Life on the playground wasn't easy either. I was always the last one chosen to play on any sports team. I was laughed at in gym because I was so much smaller than everybody, that I couldn't run as fast as everybody else. Basketball was a joke. I was always pointed and laughed at whenever I had the ball in gym class.

I was so small that the gym teacher wouldn't allow me to climb across the stall bars like all the other children. Instead, I had to

climb up, hang for a few seconds, and then climb down. So, again, I was singled out because of my height.

Take all these factors, and it's no wonder that I became a bad student. I was detached and alone most of the time, and the last place in the world I wanted to be was at school, where every child belongs. Needless to say, I spent some time during school days watching the Cubs lose--mostly--in the late '70s, for Wrigley Field was right down the street from Children's Memorial Hospital, where I began therapy--being treated with human growth hormone from cadavers.

In the late '70s, human growth hormone was in short supply, and common thought was to deliver growth hormone in the muscle, not in the subcutaneous tissue as it is done today. So when I started therapy, it was using very large needles only three times a week. This sort of therapy was rare and unknown by most.

My mother searched for information, mostly unsuccessfully. There was a small group at the time called the Human Growth Foundation--you've just heard from them--and the Human Growth Foundation, at the time, was the only organization

that offered any sort of information to the lay person, outside of the typical doctor talk that you'd hear in an endocrinologist's office.

My mother became involved with the Human Growth Foundation and quickly became the director of chapter development. She flew around the country and organized groups of people that all had children affected by growth disorders; whether growth hormone deficient, or idiopathic short stature. After some time, the direction of the organization was not exactly in line with what my mother had in mind for an advocacy group. So she decided, with a small group of other parents, to start the Magic Foundation for Children's Growth.

This organization started in a bedroom--my bedroom. I was kicked out and I had to go live in another bedroom. They started with a telephone and a typewriter. And 13 years later, they're now one of the largest organizations, and a leader in bringing advocacy and information to parents of affected children. They have members--over 12,000 worldwide--from Nebraska to New Zealand.

And while I'm here on my own today, not as a representative of the Magic Foundation but, instead, as a patient and as an advocate, I do

believe it's right that I disclose that the Magic Foundation, which does have a familial association, is funded through private donations, memberships, and grants from pharmaceutical companies, including Eli Lilly.

What being a leader in endocrine advocacy means for my mother is not glory, or a feeling of dominance in the marketplace but, instead, tears. That's right--tears. It is not uncommon for her to bring letters to me at family dinners or events. These letters usually talk about how difficult a time some child is having because they're short. And all these years I thought I had it bad, being picked on and called names. Some of the children I hear about are being physically abused or hazed on the playground and in the locker room, and are often detached from society.

When I hear of studies that conclude that short kids don't suffer psychologically because of their height I know they are mistaken. You see, these short kids have to be tough; to build up a thick skin just to have the confidence to go to school everyday. So, when they're in a study and somebody is asking them whether or not their life is different because they're short, what these kids

have to tell themselves and others is: "No, of course, I'm perfectly normal." And this comes out only after a great deal of trust and time is spent with each of these patients, may the truth possibly surface. And, in most cases, it doesn't.

Dr. Guyda referenced a few of these studies in his presentation. What I suggest to anybody who's interested to see if short kids are affected by their height is that they come to the Magic Foundation national meeting--it's next month, in Chicago. There you can meet hundreds of children-- who are being treated, and not treated--with growth hormone deficiency, idiopathic short stature and a number of other growth disorders.

In this place you can find the truth. You can see kids talking to other kids about how bad their lives are, and what they share. Because they're in a group with their peers, they feel a little bit more open and address these issues much more than they would in a clinical office space in a research study.

I lied. I've been in more than one study in my life. In fact, I've been in several studies. And whenever the question comes up how was my life, being short? Well, I don't know this person with

whom I'm speaking. Of course I'm going to lie. Kids do not want to open themselves up to that sort of interrogation in a clinical setting. It's just not going to happen.

Until that time that the truth is learned about short kids, I'm here to tell you that the conclusions are incorrect. And I'm okay with the act that my childhood was miserable until I started to reach my peers with regard to stature. I don't think most people who go through something like what I went through would be comfortable discussing the topic. Luckily, most of the kids that are diagnosed growth hormone deficient and experience a positive therapeutic course.

However the story doesn't end there, does it? What about the kids who are not technically growth hormone deficient, and do not get treated, despite the obvious need for growth hormone--to an endocrinologist, of course.

So how is it that kids can technically not be growth hormone deficient but still respond favorably to growth hormone? Well, the fact is that endocrinology, with regard to growth disorders, in many ways has yet to be discovered. Simply deciding whether or not a child is growth

hormone deficient, based on an arbitrary number--mostly set by insurance companies, as is done today--is just not good diagnostic medicine. In fact, in my opinion, it's quite irresponsible.

We need to look at the big picture. And the big picture is this. It tells us that if a patient is more than 2.25 standard deviations below the mean in height, that something is wrong, more times than not. So, forget about whether or not a pituitary stimulation test reveals true growth hormone deficiency. If a child is short enough to be off the charts, there is no reason why growth hormone treatment shouldn't be tried, if a trained pediatric endocrinologist sees a need for it.

What's great about growth hormone is that the results are pretty clear in the first year, if dosed properly. If a child responds well--great. A life is forever improved. If there is no response, at least there will never be the "what if?" question asked by the endocrinologist or a family.

What bothered me most as a child was that I was treated according to my height and not my age. At age seven, people spoke to me as though I were four or five years old. And until I was

mature enough to realize what was happening, I thought they were a bunch of really stupid people in Chicago.

[Laughter.]

Being treated according to size has been a theme I've watched throughout my life. And I've found it to be more common than it should be. For nearly three years I worked for a pharmaceutical company selling growth hormone. I visited on the average of two endocrine offices a day. What I saw day-to-day was shocking to me. Doctors and nurses treating kids according to their size and not their age. Now, imagine what this must be like in real life for a child visiting an endocrine office and being treated in this way, where endocrinologists deal with growth disorders.

The fact is that short kids are at a disadvantage. So the question is: is it right to treat someone who hasn't a clear diagnosis of growth hormone deficiency--basically, is it right to treat idiopathic short stature with growth hormone?

I say the answer is yes. It is as right as getting corrective lenses for eyesight that is abnormal. It is as right as an insurance company

paying to repair a dent in a car. It is as right as getting a tutor or extra help at school for a child who isn't performing well.

Most everything we know is measured against what we know as normal. From a statistical standpoint, negative 2.25 standard deviations below the mean falls just over the bottom 1 percent. What would you do if your child, for no reason, was learning at a rate below 2.25 standard deviation below the mean? Would you wait to see if they'd catch up? Or would you do something about it? How about your 401(k)s--your retirement plans? If your investments are performing at such a bad level, are you going to make the adjustment, or are you going to wait and see what happens?

Would you send your child to a school that was in the bottom 1 or 2 percent in the state--or in the country, for that matter? Remember, this treatment is not around for kids to get tall. It is around so kids can get normal.

So why am I speaking today? Why did I spend the money out of my pocket to be here today? This is something I've been asking myself for weeks, since I discovered this proposed indication.

The reason--truthfully--is that I'm here

to fight for all the other kids who deserve a fighting change to receive therapy that can and does improve life every day; to fight for therapy that is safe, that is abundant, well-regulated and monitored, and accepted as commonplace in the endocrine community.

Your decision today can give endocrinologists the tools to help these really, really short kids reach a somewhat normal stature. People fought for me when I needed help, and I am here fighting for those kids who need help now.

So, to borrow a line from my mother, Mary Andrews: "Please remember, before you make your decision, that children have only a short time to grow, and a lifetime to live with the results."

Thank you for your time.

DR. BRAUNSTEIN: Thank you.

The last public speaker is Dr. Sydney Wolfe, Director of Public Citizens Health Research Group.

DR. WOLFE: Thank you for having the public session, which is an important part of meetings.

I'm just going to spend a few minutes talking about the benefits of this therapy, particular for people with idiopathic short

stature; something about the risks; a little bit about the floodgate of unapproved uses that Lilly talked about in some statements it made to the press yesterday; and then just some concluding remarks by a couple people who have thought a lot about this issue, from a medical and psychological standpoint.

First, as you heard in the presentations this morning, the average in the randomized placebo-controlled trial, the average increase was 1.44 inches--or possibly less. But that's the general range. There was, as you also saw, no evidence of any psychological improvement in those who got the drug, as opposed to placebo.

I was very disturbed to hear the flippant Lilly response to the question this morning, which was: is it possible to predict who's going to have a benefit or not? And the response was: well, you can't tell whether they're going to grow two inches or four inches--quote, quote. In fact, that's way above what the average is--1.44 inches.

Other phrases that were used this morning by Lilly, whether this is a "pathologic" height abnormality, and it's difficult to withhold treatment for people such as this. As Dr. Guyda

said--and I agree--this is not a medical diagnosis but a description.

I want to just spend a little bit of time on the risks, and just complain about the fact that I believe this is the first FDA advisory committee I've ever been to in 32 years--probably 50 or 100 meetings--where there's been no FDA presentation. If they had been here, they might have made a presentation about, certainly, one of the more worrisome risks, which is pseudo-tumor cerebrae, or a condition of increased intracranial pressure, with headache, nausea, vomiting, increased pressure reflected in papilledema and the optic nerve ending. And whereas the FDA has earlier, in 1995 and 1993, published some case reports, we reviewed the database and found an additional 25 cases in children of intracranial hypertension or pseudo tumor cerebrae, for a total of 53 cases that the FDA is aware of. And many of these are four, five, six, seven-year-old children.

Aside from the problem of having three or--as Dr. Guyda suggested--possibly five or six shots a week, once the child starts complaining of headache, nausea, vomiting and has possibly some visual changes, which occur commonly, they are

subject to the same kind of work-up that you would have to do to rule out cancer. This is not cancer--repeat-- but it's a condition clinically close enough to cancer that you'd have to do an extensive work-up, including a lumbar puncture and an MRI and CAT scan and so forth.

So, 53 cases--this is as of the end of last year, and it's missing two or three years of data. So it's at least that high, and those are only the cases that are reported. It's estimated by the FDA itself that only about 1 out of 10 cases of adverse reactions are reported to the government.

I'd like to just go on to the issue--again, Lilly raised this issue in comments made in the context of this hearing, that there might be a floodgate of use of this once the barrier is down. You heard this morning that there already is sort of a floodgate--10,000 people were estimated--10,000 children were estimated to be getting this for idiopathic short stature.

This is, now, from a website from another group--not the ones you heard of, but this one is called "ShortSupport.org." It has links to Lilly for information about Humatrope, and it has links

to Genentech. Now this is the first paragraph in it, and it flies in the face of--I mean, the anecdotes you've heard, particularly the last one from someone who actually has growth hormone deficiency, are real. You can't deny anecdotes, but the reason you do placebo-controlled trials is to see how the group getting a placebo compares with the other group.

This is the opening paragraph on a website--a widely-read website, apparently: "Our society places a high value on a person's height, almost more than any other characteristic. Children who are shorter than their peers face significant challenges. They are often teased, often on the receiving end of name-calling prejudices. They may deal with their frustration by becoming depressed, angry or aggressive. If they do not experience a growth spurt they will face other challenges as adults. Parents need to be aware of these challenges so they can help their children become happy and productive." Again, the psychological evaluation in that study did not show that at all.

This page describes some of the causes and treatments for short stature children:

"Administering human growth hormone is one treatment in certain cases, but we also explore other ways that parents can help children." Only several pages into this website do you find out that that's not approved for idiopathic short stature.

Another example of the floodgate was a successful criminal prosecution of Genentech in 1999 by the Justice Department for illegal, off-label promotions; the first time there's ever been a criminal prosecution of a drug company for violating FDA rules. More recently there's been the TAP-1, concerning Lupron, but this is an early one. The company had to pay $50 million, including $30 million in criminal penalties, and $20 million in civil penalties for illegally marketing Protropin--their version of human growth hormone--for treating children who were short for reasons other than a lack of adequate growth hormone, etcetera--Turner's syndrome.

So we already have a history of criminal off-label use. There is off-label use going on now. I have no evidence whatsoever that Lilly is doing anything like this, but the point is that the floodgate has already been opened to some extent.

There would not be any--quote--"denial" of children who are already getting this if your committee decides not to approve it.

But I would strongly urge against approval. And I'd just like to close, as I said, with a couple comments from people who've written about this. One is Dr. Vos, in the United Kingdom, who said, "There's little evidence that the short but otherwise healthy child is inevitably disadvantaged or in any way missing the opportunity for individual fulfillment." She goes on to say, "Even when a child is initially unconcerned, any attempt by the parent or doctor to modify his or her appearance may signal tacit disapproval. The short child, alternatively, who has unrealistic expectations as to the benefits of treatment may respond negatively to what is perceived as treatment failure." Again the majority of these people are not going to have very much of a growth spurt. Again, average 1.44 centimeters over four-and-a-half years. So the expectations are really very different than, I think, what the reality is likely to be.

I'm going to read one more thing. This is from a paper--it's listed as a reference in the FDA

handout--from 1999, by Dr. Oberfield, a physician at Columbia College of Physicians and Surgeons. She says the following: "one may ask whether the actual gain at final height in some children with idiopathic short stature who are treated with growth hormone is of real clinical or psycho-social importance. Can we, as we approach a new era of growth hormone augmentation therapy, continue to practice medicine without responding to pressure from society, parents, or our own biases--"--and I would add pressure from the pharmaceutical industry.

She goes on to say, "I suggest we can practice and resist the pressure, and that we should heed the advice of the Greek philosopher Epictitus who stated that 'reason is not measured by size or height but by principles.'"

Finally, Dr. Vos, who I quoted before, distinguishes between efficacy--average height gain of 1.44 above placebo--and benefit. And the case she makes is that in this circumstance, even if you can measure a statistically--although questionably clinically--significant increase in efficacy, the evidence of the benefit is just really not there.

So, again, I urge you strongly not to

approve of this for a number of reasons which have been stated more succinctly than I have.

Thank you.

DR. BRAUNSTEIN: This concludes the open hearing.

Committee Discussion

DR. BRAUNSTEIN: And before going and asking Dr. Orloff to give the committee the charge, I'd like to reopen the discussion from the committee to Lilly to answer any questions that are still remaining.

[Pause.]

Yes--Dr. Watts?

DR. WATTS: We've heard that the children in this trial, by height, were no different from children with growth hormone deficiency, and that they're growth response to treatment was no different than in children with growth hormone deficiency. Clearly they had different responses to provocative tests.

Can you tell us about any other differences? Were there differences in body composition, for example--or anything--just anything other than short stature to suggest that their own growth hormone secretion or action was

different from normal?

DR. CUTLER: The main difference--and this went by, probably, pretty fast in the baseline characteristics, because this group, as a whole, did have a rather low IGF-1 level. In standard deviation score, it was minus-1.6, I think, in one of the arms, and right at minus-1.2--yeah, minus-1.5 in the placebo, and minus-2 in the Humatrope arm. And, on average, it was about, therefore, something like minus-1.7.

And this is something that's been seen repeatedly in this group of children. It does suggest that they have at least about--close to have of them actually have IGF-1 deficiency, even though the peak growth hormone tests are normal. And it's resulted in some people feeling that this should be called "growth hormone action deficiency" in some sense, because they seem not to be responding normally. Dr. Hintz likes that because that's the term he wants it to be called.

But that's the main other difference.

To my knowledge, no one has shown body composition differences, for example, in fat mass or lean body mass, or other differences of that sort, between the patients who test normally and

those patients who have the average kind of response in growth hormone deficiency, say, between a peak level of 3 and 10.

The extreme growth hormone deficient patients--those who are either genetically or very, very deficient--I think are often recognized by some phenotypic features that are well know, both morphologic and also tending to have about a half of a standard deviation higher body mass index and fat mass.

DR. BRAUNSTEIN: Dr. Woolf?

DR. WOOLF: Going through the flow chart of the pivotal trial, there were as many patients who discontinued growth hormone treatment on their own as completed the trial.

What were the reasons that these people who--these kids who were treated for at least six months discontinued the treatment?

DR. CUTLER: The main reason for discontinuation was patient decision. And in contrast to normal practice, where you're going to a nearby office, almost all of these patients were referred from great distance. So they had to make--and they were seen every six months. They had to make trips to the NIH every six months, and they

received rather intensive investigation there. You saw some of the psychometric measures, for example, earlier. And just--for some of them, it just was more than they wanted to maintain.

I would say that at the time of dropout, that the mean duration of treatment in the non-final-height group was just over three years, on average. So they did stick with us for a fair period of time, and that's probably one of the reasons there's so little difference between the broader efficacy-evaluable and the final-height. They had a lot of treatment. But ultimately they were, you know, mid-adolescence, 15 or 16, they said, "I've just been traveling back and forth, missing enough school and so forth long enough," and chose to drop out.

DR. WOOLF: Before they dropped out what kind of response to the treatment did they have?

DR. CUTLER: Umm--maybe the easiest thing would actually be to go back to the core slide, either the--I think maybe the most useful one is actually the one that has the non-final-height sub-group. It's the one right before this one--45.

So these are--these are all patients who dropped out, and therefore they're in the non-final-height

sub-group. And these are placebo patients who dropped out. And the mean difference between them, in terms of growth hormone treatment effect, was .55. It's been rounded to .6 on this slide.

The primary analysis result, which is basically here, was .51 SDS. So very similar, at least at their last observed height, to what was seen for the primary analysis.

DR. BRAUNSTEIN: Dr. Cara?

DR. CARA: Gordon, a couple questions, and then maybe a comment.

Well--we've been talking about non-growth hormone deficient short stature as a sort of part of, or in the same sort of mind-set as Turner's syndrome, Prader Willi syndrome, chronic renal insufficiency. But I think that there are significant differences between those patient population and the children with non-growth hormone deficient short stature.

One of the main issues that I've been concerned about regarding growth hormone in this group of children is the fact that when it comes to children with Turner's syndrome, for example, growth hormone can be utilized well into late

adolescence because of the fact that we are essentially controlling the timing of puberty.

If you look at girls with Turner's syndrome who have spontaneous puberty, their final heights are actually much less than those in whom we actually induce puberty. And the reason for that, obviously, is because of the sex steroid mediated effect on bone epiphyseal fusion. In children with isolated short stature, non-growth hormone deficient short stature, we don't have the luxury of being able to time puberty.

And it brings up the issue of whether or not growth hormone actually, beyond two or three years of therapy, when kids are actually in the midst of puberty, actually improves their chances of reaching a normal adult height.

Have you looked at patients that were treated before puberty versus during puberty, to look at changes of standard deviation scores, in terms of their height progression? And be able to make some conclusions about how growth hormone works, either prepubertally or during puberty?

DR. CUTLER: Yes--I thought you were going to ask me whether growth hormone advances puberty. You're really asking me to predict response

relative to puberty, and that's difficult. Because the design of the study was to basically treat to final height. That's sort of what we were asked to do.

I guess the best way to get at that might be--you're really asking me if you treated the patients longer--if you had a chance to treat them prepubertally, did they have a better response?

And over the range that we looked at in this study--and about half were pre-pubertal; about half were early pubertal, almost all Tanner 2--so the earliest stage of puberty at the start. Over the age range, which went from 9 to about 15, we actually--the limit was 16 in boys, but the oldest enrolled patients were boys who were about 15. And over that age range there was a relationship--you have to listen to this carefully--but there was a significant relationship between age and the final height over baseline predicted. So that, at first blush it looked like the younger you were the greater the height SDS gain.

The problem was that the same thing happened in the placebo group, and to virtually the same degree, so that the actually placebo/growth hormone difference really did not seem to differ

over this entire age range. There was no significant apparent effect--somewhat to our surprise. So that even boys treated at 15, who had a bone age of 13 at that point, got virtually the same benefit over the, say, placebo who were treated at the same age, as did a younger child, maybe, who was 10 or 11. And that's about the best I could say.

Over the range that we studied, we didn't see much in the way of an age effect.

DR. CARA: One of the ways that we looked at that question in girls with Turner's syndrome was to look at girls that had been started on sex steroids before--at around 13 years of age, versus after 13 years of age--say, about 15 years of age.

DR. CUTLER: Mm-hmm.

DR. CARA: And I was wondering if you had looked at the timing of puberty as it related to growth response.

DR. CUTLER: I'm going to have to ask my--our statisticians. We have done a tremendous number of analyses, and I'm not sure I remember them all. This is not one that is immediately in my memory bank. And--

DR. CARA: Again, the reason why I'm asking

this is because if you look at the data on height velocity data--it's on page 27 of the FDA briefing document--again shows that most of the gain is early on, within the first three years of therapy, and then sort of wanes and, if anything, falls below the placebo group.

It relates, again, to the question that I asked you during the first half--

DR. CUTLER: Right.

DR. CARA: --whether children that were on growth hormone and discontinued actually ended up doing better in the long run than growth hormone patients that continued on therapy and actually completed the study.

[Pause.]

DR. CUTLER: I don't think we've done the kind of dichotomous, you know, look that you're asking for. We have tried to look at a number of things as continuous variables--quite a few things.

DR. CARA: Your original slide--I think it's number--umm--59--you showed data for the individual patients--final height SDS for individual patients.

Now, this was for all final-height patients. I was wondering if you could show us a

slide, or at least give us an idea, where the completers were, so that we could get a sense of how those two groups segregated out?

DR. CUTLER: So, what you're really asking me is which of the eight patients who were the ones who discontinued early and then came back? Do I understand correctly?

DR. CARA: Right. Yep.

DR. CUTLER: We'll have to--I've forgotten that. We'll have to--we would have to look that up. I think it could be done, if you--

DR. CARA: And do you have the actual heights? Not the standard deviation scores, but the actual heights attained for the males and females in the different studies?

DR. CUTLER: I think we--yeah. I think we can get that for you--the gender effect, in actual heights.

DR. CARA: While you're putting that slide up--

DR. CUTLER: Okay.

DR. CARA: Why do you think--

DR. CUTLER: While we're getting that, Dr. Rosenfeld, I think, had a comment that he wanted to make about your question about the puberty.

DR. ROSENFELD: I think Dr. Cara's earlier points are absolutely right, that one of the characteristics of Turner's syndrome is that because of the ovarian failure there is an increased length of potential treatment time. This isn't necessary the case in the Lilly group of patients, and your point is well taken.

However, I think that very point serves to potentially underestimate the benefit from the Lilly study because, as Dr. Cutler's pointed out, the study design incorporated a relatively old group of patients. These children tended to fuse their epiphyses earlier than would have occurred if he had elected to choose to treat children, say, with the mean age of five. And the study design therefore served to mitigate some of the benefit that would have occurred.

The waning effect that you describe, as you know, we've seen in every growth hormone application, including growth hormone deficiency. And I think it was exaggerated in this study because these children were fusing the epiphysis.

So I think your point's well taken, and I agree with it. And I think that's another reason why I tend to believe that the Lilly study design

actually underestimates the potential for benefit in this group if treatment can be initiated at a more age-appropriate time.

DR. CUTLER: I have the other slide that you wanted.

Before I show this, I will say that the study was really not powered for sub-group analyses, and so there are going to be small numbers for many of these sorts of things. But there was not any apparent gender effect, and that's one of the reasons--by presenting everything as standard deviation scores, you're able to combine males and females, and it seemed--and actually, it was intended that that would be the case from the outset of the study. Because we knew it had relatively small numbers of females, but there was no major difference between the benefit between male and female; certainly no statistically significant differences.

DR. CARA: Why do you think you enrolled such few numbers of females?

DR. CUTLER: This is seen--with the exception of Turner's, every indication--and it's quite common that somewhere around two-thirds to three-quarters of referrals for short stature are

males. And I don't really know the reason for that. I think we could speculate, but--

DR. BRAUNSTEIN: Dr. Worcester had a question.

DR. WORCESTER: It goes back to the question of people dropping at. And I think you haven't looked at it, but I wanted to look at the next stage, then, of people coming back. Because, clinically, I assume that, particularly if there were finances and other things getting in the way, that you might see a number of children taking the product for awhile--and, particularly, perhaps, those that did the best, not continuing and then going back.

So I just wondered if you looked at all at the yo-yo effect of children on the hormones, off, and then back on--particularly in light of your own description of the catch-down phase that happens when children are taken off.

DR. CUTLER: Mm-hmm.

This study did not have that capability built into it. So if you discontinued, you became a discontinued patient. You weren't eligible to re-enter. So I don't have any data on that question.

But, obviously, the final-height data that we have will take into account whatever deceleration, to the extent that some of the patients did stop early, they conceivably may have had somewhat less benefit than if they had continued through to final height.

DR. BRAUNSTEIN: Dr. Tamborlane?

DR. TAMBORLANE: Yes, the other thing about this waning effect--I mean, for the efficacy group, I mean half of them dropped out by three years. So you're just going to carry forward that data. So, you know, that might be just a statistical quirk, the way, you know, you're trying to analyze these things.

DR. BRAUNSTEIN: Any other questions? Yes--Dr. Watts.

DR. WATTS: You anticipated the question from Dr. Cara, and you didn't answer it; that is, whether or not growth hormone treatment accelerates or changes the timing of puberty. And I would appreciate the answer.

DR. CUTLER: Yes. There actually was not any effect on puberty for the regimens used in this study, in either of the two studies. And I think, actually, probably the most helpful would be 239,

and then 242.

We first looked at onset--and, actually, these data have been published. And we did this is boys because there were so many more boys in the studies; the numbers of girls are so small--I could show those if you want, as well.

But this was published in the Journal of Pediatrics. And we looked at this by looking at the age at which testis volume was first measured at over 4 ml--and this would be just the 23 subjects who were pre-pubertal at baseline; and then the age at which testosterone first rose above 30 nanograms. That was measured every visit. And there were no significant differences in this.

And then we looked at the rate at which progression occurred from the time of onset. And what we found is that the rate at which testicular volume increased, and the rate at which testosterone--and I also could have done the clinical assessment of pubertal stage--and there really was no difference at all between the growth hormone and placebo-treated groups, either in the time of onset or the rate of progression through puberty.

DR. BRAUNSTEIN: Dr. Cara wanted to make a

comment on this.

DR. CARA: Yes. I think we have to be careful about how well you can assess the timing of puberty in children that are being seen every six months.

I think the other issue is--one is the actual appearance of the child, in terms of the actual onset of puberty. The other is bone-age advancement, which is ultimately the critical factor in terms of height gain and, ultimately, height attained.

I'd like to point out that in a study that we actually did with Lilly in growth hormone deficient patients, the onset of puberty was definitely earlier in children that had gotten growth hormone therapy. And what we deduced from the data was that it actually normalized the timing, whereas children with isolated growth hormone deficiency usually go into puberty late, growth hormone, if anything, normalized that timing.

And in girls, it appeared to have more of a pronounced effect in terms of the actual timing and tempo of puberty, which may explain why in girls the response is not as significant as in

boys.

DR. BRAUNSTEIN: Dr. Grady?

DR. GRADY: I just wanted to ask--I mean, again, I'm kind of worried about the risk-benefit ratio here, even if we think that benefit is an inch, a couple of inches in height.

It seems to me that your indication is fairly broad. I mean, could we treat five-year-olds? You know, is a five-year-old capable of making any kind of informed decision about whether or not they want to commit to four or five years of a daily injection to make them a couple of inches taller?

It seems unreasonable to me not to have some sort of an additional age criterion. And I wonder what you've thought about that.

DR. CUTLER: You know, I think I'd like to--I have my own personal opinion, and I do still go to clinic. But I think I'd like--Dr. Rosenfeld, you're closest to the microphone, so I think I'd like just to have one of our consultants who does this every day comment on this--I mean, their views about it.

DR. ROSENFELD: Well, the age issue is a very tough issue. We don't currently employ an age

cutoff. Or if we do, it's a very weak cutoff of two years for other growth hormone indications. And that's, in large part, because there's a recognition that a child typically, by the age of two years, establishes the percentile that he or she will grow on for the remainder of childhood--at least until the time of puberty.

I think your point is well taken that a five-year-old is hardly able to give an informed consent about growth hormone, but I don't know that that would be true at age six or seven, or eight or nine either. And I find it difficult to figure out how I'm going to differentiate a five-year-old who's minus-2.8 standard deviations from Turner's syndrome who's minus-2.8, or a growth hormone deficiency patient who's minus-2.8 standard deviations.

So, having batted this around at length with the consultants and with the people at Lille, we again felt that this was something that was best left to the domain of the practicing pediatric endocrinologist to make the judgment call that integrated the clinical setting of the patient, the particular growth parameters and laboratory parameters of the patient.

DR. BRAUNSTEIN: Dr. Follman was next, then Dr. Goldstein.

DR. FOLLMAN: I'd like to come back to something that was brought up earlier as a comment Dr. Grady made, and it had to do with in the GDCH trial, the mean duration of treatment was different between the two groups.

And in the document that--in the FDA document, it looks like it's about a half-year longer for the Humatrope patients. And I think you said it the other way around. And then, also, if you look at E001, the mean duration of the measurement of final is about a year longer in the higher dose compared to the lower dose.

So, if you're concerned about, you know, children getting taller as they grow older, and you're looking at final height at different stages--or different times relative to randomization, it seems like there might be the potential for a bias there. So I was wondering if you had looked at that and, in fact, addressed the issue of whether the final height was really the final height--you know, because it's occurring earlier in the lower-dose or placebo groups in your two studies.

DR. CUTLER: Well, let me clarify first the

point about duration. You're correct that the duration of the growth hormone treatment was longer. It was 4.6, I think, compared to 4.1 years. But the age at which their final height was measured by six months. So it was 18.6 versus 19.1.

So my earlier statement was correct, because I was referring to the age at which the final height was measured, not the duration of treatment.

DR. FOLLMAN: Do you have a similar comment for E001, then?

DR. CUTLER: Now, for the--I don't actually happen to remember the age at which the final height was measured for E001. I've looked at it, and I don't recall that they were discrepant. Does anybody have that number? Or we can get that for you, I suspect. But I don't have it right now.

There were, as always in small numbers like this, there will be some imbalances in age at randomization and so forth. We can try to get that.

DR. BRAUNSTEIN: Well, while we're looking that up--

DR. CUTLER: But I want to follow-up,

though, because I don't really quite understand the concept that--I want to be sure I understand the area where you're concerned that bias might be creeping in related to efficacy. And I also want to explain that when we--when the ANCOVA determines this SDS difference, and we then express that in a corresponding centimeter way, we do do it at a single age of 18. And in terms of whether--I guess the issue is whether one group might be nearer final height than the other. Is that the issue? That one group might still be growing more than the other in that last little bit of lingering growth?

DR. FOLLMAN: Right. The concern was that, you know, you call it final height in the placebo group, and yet they're going to be growing a little longer, perhaps than the other group was.

My real concern, I guess, was the mean duration was different. I was thinking that was related to the age at final height, and you've told me that there's not really a concern there. If anything, the placebo group is a little older.

DR. CUTLER: Yeah.

DR. FOLLMAN: So that reason for my concern about bias isn't really--

DR. CUTLER: Yes, they were six--and one of

the things we did in the design is to have an interval of a year from the time treatment stopped before we measured that. So the age of that measurement for the placebo patients, that's the mean age, which involved some girls, was 19.1. Growth is very slow at that age. And I don't have the exact numbers, but some of the values that I've looked at were height velocities like, you know, .2 millimeters a year kind of thing. They were--many of these patients had really gotten to very slow rates at the point that final height was measured.

DR. BRAUNSTEIN: Dr. Goldstein, you were next.

DR. GOLDSTEIN: By way of background, I happen to be a board certified pediatrician, and practiced pediatrics for 16 years before joining the industry. As a point of--and also, chaired the American Academy of Pediatrics' Clinical Pharmacology Section for six years.

As a point of information, issues such as consent that were raised before have, in many institutional review boards, been treated with assent rather than consent. And it is a concept that can be utilized effectively, certainly, as Dr. Rosenfeld said, by six to seven years of age.

That's probably the bottom of the--you know, I wouldn't go as far as five.

You all know what pediatrics is, and big people's doctors often call it, in a term of terribly ironic today, "midget medicine." But to that end, having practiced and having seen this for that long, do we want to wait five years to find out whether we should have made a diagnosis, or should have referred the patient for treatment? In many instances--and I think Dr. Grady quoted a figure of one in a hundred--the pediatric is the first level of filtration before even the pediatric endocrinologist gets into this. I can't tell you how many mothers--overanxious mothers or fathers I've managed to delay successfully.

But the point is that I would not want to wake up five years later, or 10 years later saying I wished I had. And many of my colleagues, I have no doubt, feel exactly the same way.

The psycho-social consequences of this are to the child, to the family and to their respective communities are often only visible or, indeed, palpable years later. So it is a difficult decision that this committee makes, but I would certainly say that given all that we've heard here

today, I would certainly recommend approval.

DR. BRAUNSTEIN: Dr. Grady, you had a--no.

DR. GRADY: No, I was just going to point out that if you double duration of treatment you double the amount of time for potential adverse effects, and you at least double the cost. If you're going to treat from ages five to 15 or 16, that's, you know, 10, 11 years' duration. And, as far as I can figure, that's--I mean, my cost estimates on the back of the envelope were quite a bit higher than were presented here. So we could be talking half a million bucks, say, for treating between five and 16 years.

And that's just the cost of the drug. I don't know how much the doctor visits, and pediatric endocrine and all that's going to cost either.

DR. CUTLER: I have just one piece of information that Dr. Follman wanted.

The mean age at which the final height was measured in the dose-response study was 18.1 years in the low-dose group, and 17.8 years in the higher-dose group. So they were very similar.

And, if I might, I would like to make just one comment, Dr. Grady, to your points about the

size of the population. I think the population prevalence is correctly stated at about 1 percent. But the numbers of children who will be treated--all of us who work in this field quite confidently know will be much less. So a realistic--if that's an important consideration, the estimates that Dr. Quigley has provided of about 40,000 children--30 to 40--from all manufacturers for this indication, five years, is our best estimate. It's a very realistic estimate. And that really amounts to 10 percent of the population, or about one in a thousand children, which we feel is a very responsible number to be treated with this condition.

DR. BRAUNSTEIN: Dr. Schade?

DR. SCHADE: Yeah, I just--in listening to all this discussion, I'm trying to really come to the issue that--the problem that I'm having, and that is: I feel that most people here believe that short stature does cause, or can cause, a very serious handicap psychologically and developmentally, and cause many problems. And we've heard, I think, some very compelling testimony during the open session.

And I also think that the data we've seen,

that growth hormone therapy does provide some increase in growth. Where I'm having trouble is trying to come up with any data--and Lilly seems to say "We don't have any data,"--that if you do take a short child and you treat them with growth hormone, what percent, or how much decrease in the psychological burden are they achieving with this expensive treatment?

In other words, it isn't that short stature is not a very serious handicap, it's what benefit, in real terms--not height--are we actually seeing with the growth hormone treatment? And that's where I'm having a problem, with understanding why we should actually spend $20,000 a centimeter, as one of the speakers mentioned--whether that's correct, I don't know--when we have--at least Lilly has not even indicated that we are reducing by 10 percent the psychological trauma of being short. That's the problem I'm having. Without any hard data in that area, how do we know whether it's worth it or not?

Maybe Lilly can address my concern.

DR. CUTLER: I think I'd like Dr. Grumbach to--just to make a comment, if you wish. I think this--we've told you the data that we have, and I

can't go beyond the data. And I think it's better, perhaps, for one of the experts in the field who does this to share their perspective.

I would say, maybe, before Mel begins though--this is--it's an issue that has been around, really, from the beginning of growth hormone therapy. It is not unique to this indication; that psychological benefit has not been shown conclusively for any of the indications. And so this is an issue that really reflects, I think, to the difficulty of studies in this field in developing children.

DR. GRUMBACH: I think you've hit on a very important point, and a very difficult question to answer.

The studies that have been done are really--are ambiguous. And let me just give you an example, just taking short kids, that if you go into the community and take a group of short children, and inquire about their own--the psycho-social aspects, you'll find they don't differ very much from their colleagues. On the other hand, if you take the group of children that have been--that come to see the pediatric, the pediatric endocrinologist, you get a very different point of

view. Here, these are children that are handicapped, or disadvantaged by their height.

Now, to find out--to answer your question, we really have to get late adolescent and early-adult data about what--in terms of outcome. I think it's really difficult, as one of the people who discussed this, to really get--as one of, in the public arena--to get children, really, necessarily to be able to convey how they feel about this.

And the issue really comes down to those who feel disadvantaged that a form of treatment is available that will increase their height. But to be able to do this for a whole constituency, it's very difficult and it has not been done to my satisfaction.

DR. BRAUNSTEIN: Thank you.

Gordon, I wonder if you would comment on--Dr. Guyda mentioned that there were seven deaths among patients with Prader-Willi syndrome. Do you know anything about that?

DR. CUTLER: Yes. Prader-Willi, for those who are not familiar, is a syndrome where there is extreme obesity. And what I know is from a mailing, and I probably--in fact, I think I should

let the agency comment on this, because I have--are you able to comment? There is a mailing that's come from--to all physicians, or at least all endocrinologists about it, and this is all I know. But what I remember from the mailing is that these were respiratory, or sudden deaths, or deaths associated with the development of an acute respiratory infection in these massively overweight children. If you've ever taken care of Prader-Willi, it's one of the most remarkable syndromes of obesity. I had one of my patients once drink a quart of barium when he went for x-ray. And they just have an insatiable appetite.

And so these were directly related to the upper airway obstruction that can occur. And the recommendation that came out with these deaths, these patients need to be very carefully monitored for sleep apnea and so on at the time of considering growth hormone therapy, and to carefully be sure that there is not a predisposition to a respiratory event such as a sleep-apneic death, or sudden death.

But, Rob, do you--

MR. PERLSTEIN: [Off mike, inaudible]

DR. BRAUNSTEIN: Could you talk into the

microphone?

MR. PERLSTEIN: I can't add anything to what Gordon just said. The agency's aware of the mailing from Pharmacia, and agrees with it.

DR. BRAUNSTEIN: Okay. We'll take just two more questions.

Dr. Woolf has one, then Dr. Cara.

DR. WOOLF: Am I correct or not that the ultimate height--extra height from treatment is independent of the age that the child is treated? Not in SD units, but in inches and centimeters, since that's what counts to the kid?

Does a younger child get more height, in absolute terms, when treated until puberty than a 21-year-old?

DR. CUTLER: What we've found is that if you look at the final height compared to the baseline height--and I think it would be the same. I have it here in SDS, but I believe it would be the same in centimeters. I'm not sure we've done it exactly in centimeters--is that baseline age was a statistically significant predictor, in that the younger that you begin treatment, the higher--the greater the gain over your baseline prediction. And that fits, I think, with--and others have

actually found this in the observational studies.

So I--it's not quite correct that it's independent. The issue is that when you actually--in our study, which is unique in having a placebo control, when you actually look for an interaction term, it is not significant. And what that means is that the placebo group also did somewhat better, relative to their prediction, the younger you started treatment--the younger you put them into the study.

DR. WOOLF: This gets back to Dr. Grady's concern of duration of treatment, the same benefit treating for three years, why treat for six?

DR. CUTLER: Yeah--and I think--and maybe Dr. Quigley will want to comment--but I think it means a lot to the child whether they--since they catch up with their peers within a year or two, whether they, you know, spend their childhood very short and then catch up very late, or whether they have the opportunity to be more close to their peers during the period of development.

DR. BRAUNSTEIN: Dr. Cara?

DR. QUIGLEY: I would also just add that if you compare the GDCH data with the low-dose data in study E001, where the did start younger, and

therefore get longer treatment, there was a greater effect.

DR. GOLDSTEIN: Gordon, actually two quick questions.

One is, in your GDCH, when you looked at IGF-1 levels across the study duration, pretty much everybody started at quite a low level; almost a level that would--quote-unquote--"entitle" them to growth hormone therapy based on growth hormone deficient criteria, if you use the recommendations that were proposed by Rosenfeld et al. In the E001 study, it didn't look like the IGF-1 levels were that low. They were in the, I think, 81 nanograms per mil range or something like that?

DR. CUTLER: Mm-hmm.

DR. CARA: And it sounded like they were pretty normal. Is that accurate?

DR. CUTLER: Can you give me the baseline data for the dose-response study? I just don't remember the actual number.

I mean, I think you're probably correct on the numbers, and I'm not sure that we did those particular numbers in SDS units.

But if you'll give me--it's a core slide. It would be, probably, about 50.

DR. CARA: Well, I'm just wondering why the difference.

DR. CUTLER: Yeah.

DR. CARA: If the populations were actually quite similar--

DR. CUTLER: We don't have IGF-1 on that particular--

DR. CARA: Okay.

DR. CUTLER: I think that the key point is that if you look at the literature for many, many studies of this condition, the IGF-1's range between about minus-1 SDS at the high end, to about minus-1.7 or 8 at the low. So the mean of our group was probably near the lower end, but within the range that others have reported.

DR. CARA: One of the things that we became aware of, and that parents actually mentioned--especially in the Turner's syndrome patients--was that there was concern about the size of hands and feet, as kids continued on therapy.

Did you notice any unusual disproportion of hand, foot--hand size or foot size?

DR. CUTLER: No, this is the first I've actually heard any mention of that. In terms of our--at least as far as--I mean, not the Turner's,

but in terms of our study patients, there's been--we didn't measure hand size, but no comments clinically that there was any change in hand or foot size that would be out of proportion to the rest of their growth.

DR. BRAUNSTEIN: Dr. Follman?

DR. FOLLMAN: One of the concerns that I think that we've been asked to look at is whether the floodgates would be open, and that there would be a large number of children treated with this if it was approved as indicated.

You have a model where you talked about 400,000 children would be eligible for this, and you anticipate only 40,000 would actually be treated. If you could briefly describe, you know, what assumptions, or how the model arrived at that number, I think it might be helpful.

DR. QUIGLEY: Thank you. The model starts with the--can I have that core slide back, too, please? No--the core slide.

The model basically starts from the prevalence of height below minus-2.25 standard deviation scores in the total population. So, starting with the total population under 2.25 standard deviation scores, we calculate 400,000

children, and that is between the ages of 7 and 15 years. And the fact that the number here is 2.25, and the 7 to 15 year age group here is included underscore what the differences are between the model that we use and the model that's actually in the--the numbers suggested in the FDA's document.

We then used the model that Finkelstein and coworkers developed in their 1998 paper that looks at the way in which growth hormone is prescribed for this group of patients. And so starting with the total of 400,000, you lose probably 70 percent or more of them at the primary care physician level. So the numbers are whittled down very dramatically at the first level.

At the second level, with respect to treatment recommendations by pediatric endocrinologists, there's another 74 percent or so--74 or 75 percent taken off what's already reduced down to a quarter of what it was when we started. So another three-quarters is chopped off down here. And then at the insurer-reimbursement level, another 80 or 90 percent goes down from the level you started with before. So that's how the numbers get down to 30 or 40 thousand out of the 400,000 we started with. And that's a well-validated model

from the literature.

DR. FOLLMAN: Of course, if this is approved as indicated, things might change--in particular the selective referral might increase, and insurance might change as well--insurance reimbursement might change.

DR. QUIGLEY: Those assumptions were taken into account in coming up with the numbers that--so these actually are numbers that include the assumption that this is an approved indication. So we've built into that the fact that there will be higher rates of referral to the pediatric endocrinologists, higher rates of approval of recommendations for treatment, and higher rates of insurance with that model.

DR. BRAUNSTEIN: Okay, thank you. We're going to take a 10 minute break then come back for the charge and then discussion of the committee, and we won't take a break later on.

[Off the record.]

DR. BRAUNSTEIN: Okay. Dr. Orloff will now give the charge to the committee.

DR. ORLOFF: Is everybody back?

DR. BRAUNSTEIN: Almost.

Charge to the Committee

DR. ORLOFF: First, from the FDA I'd like to thank the speakers at the open public hearing for their statements. The open public hearing is, like the discussion by the Advisory Committee, an important aspect of this process for FDA's function with regard to decision-making.

I've got to catch my breath. I just had to run and fill a parking meter.

[Laughter.]

The charge to the committee, as people realize, is generally to go over the questions, and I will do that. I just wanted to make a couple of comments first.

The first is that, as you will have noted, the questions cover a number of issues that have been discussed already. And we realize this. It's not unexpected. I guess it probably means we were on based with regard to our questions.

I leave it up to the Chair and to the members to extend the discuss as they choose on the questions, or to deem them covered, as it were. That's up to you.

And I remind you--the committee, that is, and those present--that perhaps more than the yea or nay vote tallies on questions that have yea or

nay answers, FDA benefits from and relies upon the content of discussion around the issues. In other words, we are listening, and have been.

The questions are our best efforts to get to the major points requiring comments. We also note that additional points have been raised, and they've been heard by us.

And then, finally, I want to just--before I go to the questions--I just want to raise one other issue that has not actually been raised here explicitly but may be in the back of some people's minds, and in the minds of those perhaps listening from the audience. And that is, to some extent it's kind of the flip side of the clinical significance question that's been asked and will be asked again, and that is whether the use of growth hormone in non-growth hormone deficient short stature represents "cosmetic" use of growth hormone and, as such, might be construed, were it to be approved and endorse, might be construed somehow as setting a broad precedent for cosmetic use of drugs.

The first point I'd like to say is that any decision that's made with regard to growth hormone in this instance will be based upon a

judgment of a favorable balance of risk versus benefit for the proposed indication, and that would not, in our minds, be setting a broad policy with regard, generally, to the use of drugs for cosmetic purposes.

I'd also propose that it is not the purpose of this meeting to debate the merits of approvals of other drugs for what some--usually those unaffected by the target condition--might construe as cosmetic purposes. And I think it's safe to say that we should concede that once demonstrated to be safe and effective, the choice of whether to attempt therapy for, for example, baldness, or mild acne, or even overweight is up to doctors, patients and their families as they weight the potential benefits of the therapy against the potential risks.

And I guess I said it before, but I'll just point it out one more time: that we don't see a regulatory stance favoring approval for the use of growth hormone putting this Division or the agency on a slippery slope toward blanket uses of--cosmetic uses of growth hormone, as well as for other drugs.

So, some of the questions--I guess I'll go

quickly over the ones that I think don't need much clarification, and pause to clarify some that I think do.

"Has the efficacy of human growth hormone, or Humatrope specifically, in non-growth hormone deficient short stature been sufficiently characterized?" And I think it's worth our hearing the committee's opinion on, really, the matter of whether proof of principle of efficacy in this population has been provided. I realize there's been a lot of discussion about the absolutely magnitude of the effect observed, as well as what could be expected, depending upon a number of variables. Has proof of principle of efficacy been characterized?

"Is the dose regimen proposed supported by the results of the studies presented?" And a very important point here that has been the subject of some discussion so far--and I leave it again up to you to discuss it further if you like--comment on the discussion by the sponsor of the importance of height augmentation in the target population, and on the conclusion that the expected effects are, indeed, meaningful. I wrote "clinically meaningful," but I think "clinically" is a

problematic term here. "Meaningful" is vague, but I think it's the best we've got.

"Has the safety of Humatrope in non-growth hormone deficient short stature been sufficiently characterized? Specifically, do the results of the trials and the current knowledge of the safety profile of growth hormone in children support a favorable balance of risk versus benefit in this population?" And also, something that wasn't elaborated on in great detail, I believe, by the company, we're interested in your thoughts on the proposal--or the possibility, you'd say, of long-term follow-up of these children as part of GeNeSIS; and what other suggestions you might have with regard to surveillance of the safety of this intervention in this population. And I know that the company is prepared, if need be, to give a little bit more explanation on, actually, the details of their GeNeSIS program, and on its present and future, I gather.

"Are the available data from the studies presented sufficient to guide the safe and effective use of Humatrope?" And this is a distinction from "Is there evidence of safety and efficacy?" Do we know enough about how to treat

kids who have non-growth hormone deficient short stature from the studies that have been done so far--and whatever other knowledge people might bring to the clinic--to guide the safe and effective use of Humatrope in this population?

And some of the sub-parts of this question include: "Is the restrictive height criterion that is proposed satisfactorily rationalized?" Is it too high, is it too low? Do you have any comments on that.

And perhaps more importantly, "Are there additional criteria needed, such as pre-treatment height velocity, bone-age, chronological age, serum IGF-1 level, growth hormone receptor mutational studies, to avoid unnecessary or, as it were, potentially ineffective growth hormone therapy in children who have idiopathic short stature?"

I think it's also been noted--and we noted--that the range of responses observed in the trials, and thus expected in the clinic, is broad. Additionally, there's been a dose-response demonstrated. The question is--and we'd like to hear discussion on this, we do not expect definitive plans--we'd like to hear discussion on "The need for information on the effective

individualization of dose, age at initiation of therapy and duration of therapy on growth response and on safety."

And what I'm driving at here is the idea that, irrespective of what we--the decision the FDA finally makes on this and, frankly, irrespective of what the advice of the committee is today: what more is needed going forward in this field? Perhaps you might--some might judge that there are certain things that are absolutely needed before we could move forward with an approval. You're welcome to comment on that. But even if you recommend approval, I think it's quite clear that not all the questions about the safe and effective use of this intervention in this population have been answered by the studies to date. So, with the realization that further placebo-controlled trials in this area are not possible--but, I believe studies as a generic term are possible--what additional information needs to be gleaned from such studies?

And, likewise, we'd like to hear you--or, following that we'd like to hear you discuss the "Need for information on potentially useful predictors of response, both pre-treatment and on

treatment; for example, early growth or other bio-marker effects?"--again, to enhance the safe and effective use.

And then, the last three questions are to "Comment on the sponsor's overall risk management proposals," which I don't think have been broadly discussed as yet; and "Any other concerns you have regarding safety and efficacy."

And then, finally, the--I guess for those who are watching this from afar--and perhaps for the company a very important questions: "Do you recommend that the use of growth hormone in non-growth hormone deficient short stature, as proposed by the sponsor, be approved by FDA?"

And I turn it back. Thank you.

Committee Discussion

DR. BRAUNSTEIN: Thank you, Dr. Orloff.

I think what we'll do is we'll start with Dr. Follman, and ask him to respond to Question 1, and also A and B. And then we'll go around the room with the committee members. And then we'll start Question Number 2, with Dr. Grady.

So--Dr. Follman?

DR. FOLLMAN: Thank you.

So--to begin, question 1 has to do with

whether or not the drug seems to be efficacious in increasing height? And do I agree with the dose range that was proposed by the sponsor?

The two studies that we've looked at in detail today were both controlled studies and randomized studies. The first one was a placebo-controlled study. It was designed to compare the final height between the two groups.

It had a lot of dropout which was somewhat concerning to me, and I think also to the sponsor and to the FDA as well; and it was subject to many different analyses. We heard discussion of the different cohorts that were used; the efficacy-evaluable; the final-height cohort. And there was a consistent message, I think, in the analyses there that the treatment effect seemed to be significant for a variety of analyses.

The magnitude of the effect seemed to be about 3.5 centimeters, maybe and inch-and-a-half--something like that.

So I'm willing to say that, on the basis of that--even though there was a lot of dropout and we don't like that--the treatment seems to b e effective in increasing final height.

The second study, that looked at different

doses and different dosing schedules of Humatrope also showed a benefit, in terms of the pre-specified primary endpoint, which was change in height velocity over the first two years of study. They also looked at final height in that study, even though it wasn't the primary analysis, and the results that they showed demonstrated a trend toward benefit towards the higher-dose group.

So, in my mind, I think it's pretty clear that compared to the placebo the treatment is effective, and the estimate of effectiveness that we've been bandying about--1.5 inches, perhaps--is probably a little underestimated if we take into account the E001 study, which shows larger benefits--partly because, I think, the doses are given earlier and they're given at a more frequent rate.

So, to Question 1.A, I think the answer is: yes, it's been shown that it works in this population.

And if I have to comment on Question 1.B, what's meaningful increase in height, I think that's a very difficult question. When I first was looking at this, I thought, you know, an inch or two would be meaningful. If you're going from five

feet to 5'2", I thought that would be worthy--you know, that it would be worthwhile. And so my--what I think is meaningful, I think, is on the rather low end of what's been discussed here today.

DR. BRAUNSTEIN: Thank you.

Dr. Grady?

DR. GRADY: Well, I think the question we're discussing is: has the efficacy been well characterized and proven?

And, you know, just to summarize what was just said, I think that we've been shown that treatment with growth hormone can improve height, but that the effect is, I think, fairly small; on the average, about one-and-a-half inches; and that there's been no demonstration of the impact of this on quality of life.

DR. BRAUNSTEIN: So, you're answers to this would be: yes, it's been shown to be efficacious, and the importance of height augmentation is open to question--whether this is clinically significant because of quality of life issues. Is that right?

DR. GRADY: Well, that, and I think--I mean, I think all of us would agree that if you could change adult height from five feet to 5'6" we'd be less concerned. But changing it from, you

know, five feet to 5'1-1/2"--there is more concern that that will translate into a real impact on, you know, a person's life.

DR. BRAUNSTEIN: Okay. I think the efficacy has been demonstrated by the pivotal study, in comparison to the control group. I do think that a dose-response relationship has been shown by the European study, as well as some of the studies that have been reviewed by the meta analysis. So I do think that it is efficacious.

In regards to--and I think that the dose regimen proposed is supported by the results of the studies; and then certainly the higher dose seemed to give a higher effect than the lower dose.

In regards to the clinical importance, I think this is the crux of the problem that many of us are having with this. Dr. Grady nicely brought out that there's no really good evidence that one-and-a-half inches or so is going to improve quality of life. I'm also concerned about the resource allocation issues, about who's going to pay for this and the potential worsening of the drag on health care dollars over time.

Nevertheless, I don't think that's really the charge of the committee. The charge of the

committee is really to determine whether this is safe and efficacious, and clinically important.

So my conclusion about the clinical importance is that it really has to be defined by the patient and the parents, and that this really requires a fully informed consent of both the patient and the parents, so that they know that this is going to be--going to require six shots to seven shots a week; that the shots will be given for, potentially, 5 to 10 years--obviously, the younger--well, the data supports that the younger you start it the better the overall effect; that the individuals may not experience any improvement in height, or they may experience height improvement of one to, maybe, three inches--some individuals had a spectacular response, but most did not.

So, I think that when the patient and the parents are fully informed about this, and when they understand the resources that are going to have to be allocated, either from their pocket, or from other sources, that in the final analysis it's they, along with their physician, who should make the conclusion as to whether it's clinically meaningful or not.

So, I do think that for some individuals one inch, one-and-a-half inches may be clinically meaningful. For others it won't be, but they have to make that decision.

Dr. Cara?

DR. CARA: In terms of the efficacy of Humatrope in non-growth hormone deficient short stature, I think it's been sufficiently characterized. I think that we've tried to squeeze the data as much as we can. And the data is the data. And I think it just highlights the fact--I think the study highlights just how difficult it is to do very long-term studies, even in very motivated patients, when such frequent follow-up, and such long-term care is required. It's not only hard for the endocrinologist, but obviously very difficult for patients.

I think that in my mind, the dose--anything less than .37 as a recommended dose really does not work well. And I don't think it's advantageous to recommend a dosing range. I would simply go with the higher dose and recommend that the higher dose be used.

I think that the safety has been demonstrated. And, personally, I don't have any

problems with a higher dose. If you're going to use growth hormone, I would advise that, rather than starting with lower doses.

In terms of the importance of the height augmentation, taking care of patients that I struggle over because of their short stature and my inability to do anything for them, I think that the demonstrated efficacy for the higher dose is significant. And what we're talking about is the difference between a young girl--if we take the average response in the final heights of the patients, what it means is that for a young girl, treatment with growth hormone makes a difference of being 4'10-12" versus 5'1"-5'1.3". For a boy it means the difference between 5'3-1/2" and about 5'6-1/2". So, I think that's significant.

At loser doses I don't think that the efficacy or the height augmentation is significant enough to warrant that dose.

DR. TAMBORLANE: I also feel that the efficacy has been well established. I see the pivotal study as sort of the worst-case scenario, in view of the older age, the three times a week administration, and the lower dose. So that just--it's strength was the placebo-control aspects; that

the real dose finding experiment was the E001 study, where you're talking about two to three inches increase over predicted height. So I think that is a very efficacious response for just what Jose mentioned.

As far as clinical meaningfulness, I think that we would be very remiss not to comment--and Jose was just starting to get into that--and the incredible dedication that families, and the debt we owe to families who participated in the pivotal study; the fact that they would agree to be in a placebo-controlled, three times a week injection regimen study just, really, speaks to how important this is to them, or was to them. And I think it's the same importance that most kids who have heights who are almost 3 standard deviations below the mean really feel the same way--and we heard about that from the open public forum.

DR. BRAUNSTEIN: Thank you.

DR. SCHADE: Relative to the first question, I agree with the rest of the speakers. I think that the drug does--that they have convincingly shown that you do gain height.

Relative to the second issue about whether it's clinically meaningful, clearly, because of

the--there are dropouts in both studies, to some families it wasn't clinically meaningful. But, again, as my colleague points out, they may have been in a placebo arm, and that's always a concern in a clinical trial.

What the question, I think, really says, or asks, relative to whether the sponsor has shown or suggested by the data that it's clinically meaningful, I really think there should be additional data on some type of benefit besides simply the height. Now, I agree that if the height was dramatic--six inches--you probably wouldn't have to show anything else. But because the height benefit is much smaller than that, I am concerned that here is a very expensive treatment, in which the benefits are not clearly shown.

And I appreciate the argument that these benefits may be very difficult to show. On the other hand, I've been--and everybody on the table has been in clinical trials where you hire experts to try to get at these problems. And there are many ways to do that. And I believe that that part of the studies have not been adequate in order to show a real benefit here.

DR. BRAUNSTEIN: Thank you.

DR. Woolf?

DR. WOOLF: I'll echo what everybody else has said about 1.A. I mean, the statistics are the statistics, and no matter how we slice it and dice it, the numbers come up the same, and Humatrope causes statistically significant increase in growth.

To me the big issue is: is it clinically meaningful, and there I guess we have to say we have no really good data to support that. And I don't think I can answer this question without having some answers for some of the questions further down the list, like who should we select, and how should they be followed? And I think they go together.

I would not like to see a blanket approval on the hope that someone could grow four or five inches and, in fact, only grow one--even if it's informed consent.

DR. BRAUNSTEIN: Dr. Gelato?

DR. GELATO: Well, I would say the same to 1.A. I think that efficacy has been shown. I agree with Dr. Cara that I think if you're going to do this you should go to the higher dose, because I don't think there was much gain at the lower dose,

particularly in this patient population.

I also think that the study was hampered by the fact that these were older children. And if we look at the growth hormone deficiency experience it does certainly look like if you start earlier you get a better effect.

And I'm torn, as everyone else is, with the B part of this, in terms of what is clinically meaningful. And I'm not sure that I can answer that either. I think for the child--again, if someone's 4'9" I think it probably is clinically meaningful to be 5'1". So it's a very difficult call.

And I agree that the studies really didn't help us answer that. So it either becomes an individual thing, or it's one where, as we get farther on, maybe it will become more apparent. But, in my own mind, I'm still torn by that.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: I think the company has done everything possible to answer the questions raised by the previous committee. But I still have questions that weren't asked by the previous committee.

Efficacy, in terms of height gain, I think

is convincing. Whether or not that's the right measure of efficacy I think is the question. And it seems to me, with a drug that's expensive, with a condition that potentially affects, by the sponsor's estimates, 400,000 children, that it should be possible to be placebo-controlled trials looking at clinical endpoints. WE don't accept surrogate endpoints for agents that lower blood pressure, or cholesterol, or improve bone density. We want to see clinically meaningful results. And I don't think I can answer 1.B--whether or not this statistically significant gain in height is clinically meaningful across the board. But if 1 percent of all the students in elementary school, and in middle school are below the 2.25 standard deviation level, it should be possible to recruit one out of a hundred of them, and have vans that go around to the schools and measure psychometric response to patients who are on placebo or on active therapy.

And whether that's done as a requirement for approval, or as a Phase IV investigation, I think it's very important, if we're going to spend this much money on a treatment, that we know that it has a clinically meaningful effect.

DR. BRAUNSTEIN: Dr. Worcester?

DR. WORCESTER: I would agree with other people, that we certainly have seen in the studies we've seen that the treatment is effective as measured. As I was reading in the material, and certainly as I've been listening to things today, though, I have felt it was very much a case of where the statistics don't always translate to what it means for real human beings.

I think the testimony we've heard, and probably from everybody's own experience, we know the enormous hurt and pain of the stigma of extreme shortness. And I think the kind of changes we've seen here don't address that. So I'm leaning on the side of thinking that we've heard that, clinically, this much change in height is not enough.

I'm particularly concerned that we have a product here where there's going to be a huge difference in individual's response, and so there will be a lot of disappointment. So I think we have to really look at the medication, plus social-economic issues.

DR. BRAUNSTEIN: Okay. Thank you.

We'll go on to Question 2, and we'll start

with Dr. Grady. Yes, 2.A and B, also.

DR. GRADY: Let me start off by saying that I think safety is, of course, a very important issue here, because what we're talking about is treating otherwise perfectly normal kids who are short, for five to maybe 10 years, at a time when they're young children, up until their pubertal--potentially a critical time for later events.

I think we have data from the treatment of children with growth hormone deficiency which is fairly reassuring. Clearly the best data for this specific indication would be from a placebo-controlled comparison. And there we have data from one trial in '71 children with about--way less than 50 percent follow-up.

Nevertheless, if you look at that data, I find it a little bit bothersome. There was one death reported in the treated group versus none in the placebo group. There were five serious adverse events versus two. Three was this report of a desmoplastic tumor and Hodgkin's disease. And if you look at the adverse events, there was report of more flu-like syndromes, more infections, more pain syndromes, more bone disorders, lymphadenopathy, reproductive abnormalities, fungal and parasitic

infections and surgical procedures.

These weren't statistically different but they were fairly different. There was more than a twofold increase in those things in the treated group.

And then we've heard these other sort of concerns about issues that we have no data from these trials on, including, you know, pseudo tumor cerebrae and so forth; slipped capital femoral epiphysis, of which there was one report.

So, I don't think we have really good data on safety. And I personally think we should have really data on safety because we're talking about treating what are otherwise perfectly normal children--who are short.

DR. BRAUNSTEIN: Okay. So you do not feel that the safety characteristics have been sufficiently characterized in this group of patients.

DR. GRADY: No.

DR. BRAUNSTEIN: Okay.

DR. GRADY: And I realize that this would be a very difficult thing to do. On the other hand, I don't think it's been shown.

DR. BRAUNSTEIN: And what about--so do you

feel the risk-benefit ratio is adverse?

DR. GRADY: I don't--I don't know how to answer that, because we know the benefit, in terms of, you know, a couple of inches of height. And we have otherwise very little information, I think, on, you know, quality of life-type benefits, and inadequate information on safety.

DR. BRAUNSTEIN: And what about the proposal for long-term follow-up of these children as part of the GeNeSIS study?

DR. GRADY: Umm--well, I'd kind of like to hear a little bit more about that. But, certainly, I think if we decide to approve this there should be an effort to gather long-term safety data. This is always a difficult thing to do because there's no good comparison group.

DR. BRAUNSTEIN: What type of surveillance would you recommend?

DR. GRADY: Umm--you know, I think, at a minimum, there should be some sort of registry for patients using growth hormone for idiopathic short stature. Again, it's not a great way to get good information, because it's difficult to know what the comparison group is. But I think there should be some attempt, in addition to a registry, to have

routine follow-up of at least the first cohort of patients for specific conditions.

DR. BRAUNSTEIN: So do you think that should be a mandatory registry?

DR. GRADY: Ahh--I think there should at least be a mandatory registry, yes.

DR. BRAUNSTEIN: Okay. Thank you.

Okay. I think the safety has been reasonably well characterized. I am pleased that there's a lot of data out there in other conditions for which Humatrope, and other growth hormone preparations from other manufacturers, have been used. So I do think that we pretty much know the major problems associated with growth hormone. Clearly, as you increase the population of patients that are going to be exposed to this some small problems may come to the forefront, and we may see some problems that were not previously apparent.

I do think that in regards to risk and benefit, again, because there is a dearth of information about the psychological, psycho-social benefits--other than anecdotal information--that it again comes down to a personal decision on the part of the patient and especially the parents, since this will be started during childhood in most

individuals, to know what the potential benefits are or may not--what benefits may not be there, and what the risks are, and to let the parents and the child say, "Yes, the benefits or potential benefits outweigh the risks" for that particular individual.

As far as long-term follow-up is concerned, I think that the GeNeSIS system--what I know about he GeNeSIS system seems to be very adequate. I do think, though, that because the risks in this population have not been as well characterized as we'd like, and the benefits in this population have not been as well characterized as we'd like, that there should be a mandatory registry, mandatory surveillance of these patients.

And since Lilly has indicated that the distribution of the drug will be so tightly controlled, clearly they have the capacity to make this a mandatory part of the distribution of the drug, because people who do not provide the information or the follow-up information would not be able to get a renewal of the drug prescription.

So I think that they have a perfect system in place to have a mandatory follow-up. And this, again, should be indicated to the parents on the front end, that this is a mandatory part of the

whole program.

Dr. Cara?

DR. CARA: Bill corrected me--the data "are" the data. I got stuck between the data are the data, and it is what it is.

I also concur with Bill when he said that I think--and as Ron also pointed out--that we're probably looking at the worse-case scenario because we are, in fact, dealing with the older population of patients, significant dropout rates, and I still think that there are a lot of questions that need to be resolved, but we're definitely looking at a subset of patients that are probably the patients that are giving us a very minimal idea of what is possible.

In terms of the questions: has the safety profile been sufficiently characterized? Yes, I think so. Based on what we know about growth hormone, previous experience with growth hormone, and the data that's been provided by the sponsor, I think that the safety profile has been sufficiently characterized.

I think that there is a favorable balance of risk and benefit. I think the benefits outweigh the risks significantly. That doesn't mean to say

that growth hormone treatment should be used cavalierly or indiscretionately. I think that monitoring is a good idea. And I think that the GeNeSIS system that's been proposed by the sponsor makes very good sense.

I would extend that to--I'm not sure how you can enforce, but to try to enforce pediatric endocrinologists that are treating patients with non-growth hormone deficient short stature to provide at least a yearly update on the patients that they are treating, in terms of safety profile, in terms of their overall evaluation of efficacy, and whatnot. I think that that would make a lot of sense.

There are still a lot of questions that we have, but I don't think that the GeNeSIS sort of monitoring regiment proposed by the sponsors is going to answer those. I think those will be done by separate clinical studies.

DR. BRAUNSTEIN: Dr. Tamborlane?

DR. TAMBORLANE: Yes. As far as the safety profile, I think we have abundant experience with growth hormone in a variety of circumstances, over many years. So I think the safety profile is reasonably well characterized. In fact, I would

contend that the argument from the company, as far as--you know, that growth hormone has been used for various indications related to growth augmentation not related to treatment of underlying disease is actually, from a safety viewpoint, even more of a problem with the other conditions. Growth hormone deficiency, renal failure, Turner's syndrome--I have more safety concerns with use of growth hormone say, for instance, in Turner's syndrome than I would have in a non-growth hormone deficient child.

And I think the data that I saw actually supported the idea that there were fewer adverse effects, and I think that would be expected.

Now, the couple years I've been on the committee I've always enjoyed Dr. Grady's comments. However, I have to say, I could just envision a deja-vu from 10 or 15 years ago, if this committee was talking about a weight reduction medication for children who were overweight, and Dr. Grady's mother saying that, you know, these are perfectly healthy children except they're fat.

You know, so I really don't--I'm not sure that these severe growth hormone--or short stature patients really fit into that category. And I

think I would tend to weigh on the idea that we may not have discovered all of the psycho-social implications of being severely growth impaired at that age, but that they are, in fact, real problems.

DR. BRAUNSTEIN: And what about the follow-up?

DR. TAMBORLANE: I think the--you know, all the companies have routine sort of post-marketing surveillance. I don't understand the legal implications of mandatory involvement and follow-up. I mean, I think under HIPAA rules, you know, does the patient have to agree to be part of a registry to get the medication? You'd have to explain that to me. I don't know that it has to be mandatory.

I think the way that it is, where it's worked very efficiently with pediatric endocrine practices, where the companies actually help support the process and the data get collected.

DR. BRAUNSTEIN: Okay.

Dr. Schade?

DR. SCHADE: Yeah, it's always a pleasure to disagree with Bill.

I think we're all a product of our

experiences, and I'm an adult endocrinologist, and I've sort of lived through the rezolin era, in which the FDA approved the drug, and not until we used it in thousands of patients with diabetes did we really see some adverse events that then resulted in withdrawal of the drug.

My concern is that the use of growth hormone in the population we're talking about is a major change in numbers. All of a sudden we're going from several limited populations to a huge population that will always be huge because it's defined as a statistical standard deviation below the mean. So we're never going to reduce that population, and so we're always going to be dealing with 400,000 individuals or more, depending on how big a world you want to treat.

The other thing that influenced me besides that type of history is: growth hormone use in adults--in fact, as in the elderly--has recently been looked at, and is still being looked at. And in those individuals, although the dosages and the size of the individuals are different, there have been problems, and adult endocrinologists are concerned with those problems.

So I think there is a potential to run

into several types of problems when you give, basically, an individual with normal growth hormone levels--and we can argue that--but we're adding a hormone that's already there, rather than a hormone to growth hormone-deficient individuals, that you can get into problems. And you don't see these problems until you start treating thousands of individuals, and then all of a sudden you start seeing some problems that you didn't see before.

I guess I"m concerned about the numbers we're seeing in the clinical trials. I would have much preferred numbers in the thousands. When we're dealing with a population of 400,000 individuals that are potential for treatment. And whether we end up with 40,000, or 100,000 people, depending on the algorithm you want to use, we're still talking about hundreds of thousands of individuals. And to have clinical trials that only have hundreds of people in there, rather than a couple thousand, to me is difficult for me to understand. Because, certainly, it can't be a recruitment issue; not when there's 400,000 individuals there that are potentially treatable.

So I'm concerned that we haven't looked at enough individuals in order to define the hazards

of this drug. So whatever the FDA decides, I believe that close monitoring is absolutely required, because I am concerned you will start seeing a significant risk profile once you start treating the numbers of individuals that I think are going to be treated with this medication if this drug is approved for that purpose.

DR. BRAUNSTEIN: Thank you.

Dr. Woolf?

DR. WOOLF: Let me echo what my esteemed colleague on the right has said.

We're now proposing to treat growth hormone-sufficient children with growth hormone for perhaps a decade. And we really don't know--at a time when they're growing. And we really don't know, down the road, what will happen to these kids. I doubt whether the growth hormone will initiate new tumors, but kids who already have tumors could their spread be worse? Could this child with Hodgkin's, who was missed six months earlier--that Hodgkin's get accelerated by virtue of the growth hormone treatment? I mean, I have no idea. I don't know if anybody else has.

Certainly, in the small context of the clinical trial I think the safety was demonstrate.

But when it gets out into the field, I don't know. Certainly it's reassuring, from other growth hormone indications, that it doesn't appear to be serious--there were some problems with the adults that were overdosed, and many of those went away.

But tumor genesis still persists. So, for that reason, I think doing whatever is legally possible to have as much of a mandatory registry, with follow-up--assuming that it's HIPAA-compliant, and compliant with other regulations--would be very beneficial, and it would need to be done for decades.

DR. BRAUNSTEIN: So, do you--is your response about the current knowledge of the safety profile--do you think that that's--

DR. WOOLF: I think what we have is fine. What we don't have--we don't know what we don't know.

DR. BRAUNSTEIN: Let me go back also to Dr. Schade just to have you define that.

Do you think, with the current knowledge, that the safety profile gives a favorable balance of risk and benefit?

DR. SCHADE: Well, I only believe that's true if you're defining benefit as growth. I would

prefer that question be growth, rather than benefit, because we've already have the discussion and argument: what benefit means. So, right now, I don't think we have the data to answer that question in the affirmative. But if you want to change the benefit to the word "growth," then I would agree. But if you don't, then I cannot--I would not say we have the data to answer that "yes."

DR. BRAUNSTEIN: Thank you.

Dr. Gelato?

DR. GELATO: I think, in terms of safety profile, we do know a lot about growth hormone. We certainly know a lot about the effects of growth hormone in growth hormone-deficient children--and adults, actually. And there it seems to be safe, and there's a lot of long-term follow-up.

I agree with what has been said by Dr. Schade and Dr. Woolf, that in sufficient patients it may be something different. And certainly there are some indications that it may be. However, I think what was presented is somewhat reassuring, because there wasn't anything that at least looked like an immediate red flag.

But I do agree that whatever surveillance

goes on should be mandatory, simply because now you are going to be going out to a much larger population, treating potentially many more children, and we really don't know what's going to come down the line in 10 or even 15 years from this therapy.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: My answer to 2.B is: yes, there is a need for a registry or some type of very long-term follow-up.

My answer to 2.A is: no. In looking at the data that we have, there were 80 patents enrolled in the higher-dose growth hormone group in E001, and 13 who were followed to final height. And there's no placebo group in that study.

In the placebo-controlled trial, which was a lower dose, we have 10 placebo subjects who were followed to final height. And the comparison is not with normal healthy children, the comparison for adverse effects is with patients receiving growth hormone for other indications.

And so even in the short term, I'm not convinced that we have adequate data on safety for this indication. And I'm not sure that we know that right dose. In looking at the height

response, it appeared to me that at least half the children who received the lower dose of growth hormone did quite well, and I would love to see a dose escalation study to find out how many children--while we're told that there are no predictors of response, but in a larger trial it might be possible to establish either predictors of response, or find out who would have a maximum height response to a lower dose and which children need a higher dose, and what safety issues emerge when treating large number of children with a higher dose--things like insulin resistence, changes in glucose metabolism that we don't know about.

DR. BRAUNSTEIN: Dr. Worcester?

DR. WORCESTER: I would answer the question by saying in this particular situation we can't possible have enough safety information because we're looking at marketing this to a very large number of healthy people, at a very important stage of their development, in terms of both pre-puberty and very young. So I think the safety standards have to be high, even though I think the beginning information that we have today looks promising, but I would only think it looks promising for the

reasons that other people have said.

And obviously you would expect me, then, to go on to say that long-term follow-up, with as much information as possible, is certainly going to be necessary. So I certainly support a mandated registry--and not just while people are being treated, but also 10 years after, to see any long-term impact.

The other issue that I brought up earlier, and could not be addressed because of the kind of studies we had today, I think we're going to see a lot of people--a lot of children--in and out of treatment. And so the yo-yo impact I think is a whole other issue that we haven't even mentioned, except for my question today. And that's something else to watch for.

DR. BRAUNSTEIN: Good. Thank you.

DR. GOLDSTEIN: May I comment?

DR. BRAUNSTEIN: Umm-I need a ruling on that--since you're not a voting member of this.

DR. GOLDSTEIN: Right.

DR. BRAUNSTEIN: Dr. Goldstein has requested to offer a comment. Can we hear his comment, without a vote?

DR. GOLDSTEIN: The comment I would make

would be in response to Dr. Schade, particularly. There were--I don't recall the number, but in a hundred or two in these studies--in these rigorously conducted studies over a long period of time--if we were to wait to approve this until "adequate"--quote-unquote--safety data were obtained, as a practical matter the cost of mounting a study of thousands of patients of this prior to approval would make it, in a word, impractical.

I think the alternative of a careful monitoring system, such as GeNeSIS and the very careful pharmacovigilance and other activities that Lilly is renowned for is likely to provide a lot of the data over the coming period of time, as to be able to reassure the committee.

So I think that's a reasonable balance.

Thank you for permission to comment.

DR. BRAUNSTEIN: Thank you, Dr. Goldstein.

Dr. Follman?

DR. FOLLMAN: Yes--in terms of the safety-benefit ratio, I would say--I would vote in favor of a favorable risk-benefit for Humatrope. I think it's been sufficiently characterized in these studies. You know the studies have small numbers.

We don't really see anything alarming there. If you also take into account the other studies in which this has been studied, I'd have to say that it's been sufficiently characterized.

Of course, you know, the concern I think a lot of us have is that these are relatively small populations and now we're talking about broadly--broadening it quite a bit, so it will be tens of thousands of patients who potentially get this. And in a situation like that, things that weren't detectible earlier because the studies were relatively small, now have a chance to be detectible. And I think it's important, as has been mentioned earlier, to have a monitoring program--if it's approved.

DR. BRAUNSTEIN: Thank you.

Okay, I'll start with Question Number 3: are the available data from the studies presented sufficient to guide the safe and effective use of Humatrope in patients with NGHDDS?

And I feel the answer to that is yes, based not only on the small studies done by the sponsor, and the meta analysis, but also because the large experiences available from other patients who have short stature that is not due to growth

hormone deficiency; so--the Turner's patients, Prader-Willi, renal insufficiency patients, etcetera, as well as the growth hormone deficient patients. I think that a lot has been learned from those patients.

And so I do think that it's reasonable to suggest a .37 dose, with six to seven shots a week. And, over time, I'm sure, as we learn more about this, that would be modified.

The sponsor has proposed a restrictive height criterion for treatment eligibility. Is this proposal satisfactorily rationalized?

Ahh--I think so. And the reason why I'm hesitating is because we're dealing with a statistical issue here. And clearly, if we treat the entire population who is in the first percentile, we're still going to have huge populations in the first percentile, because by definition there's always going to be somebody who's going to be at the lower end of the curve.

But I do feel that, taking into account the learned society's recommendation that less than 2 standard deviations be considered short, and the need to be even more conservative, the sponsor has justified their choice of minus-2.25 standard

deviations.

Are additional criteria needed, such as pre-treatment height velocity, bone-age, chronologic age, serum IGF-1 levels?

And I think the answer to that is yes, and I would make this part of the mandatory follow-up program. We want to get as much data--oxyological, biochemical, bone-age data as possible, because over time we may be able to use that database to better define how the drug should be used, and in what group of patients the drug should be used.

So I advocate actually requiring that information on the front end, before starting a patient on therapy, and then collecting that information periodically while the patient's on therapy, until it is deemed that we have a sufficient amount of information to know how to use the drug effectively and safely.

C--the range of responses observed in the trials, and thus expected in the clinic, is broad. Additionally, a dose-response is evident. Please discuss the following: 1) the need for information on effective individualization of dose; age at initiation of therapy; and duration of therapy and gross response and on safety.

I think the data with this group of patients, as well as with other groups of patients, is that the younger the patient the better the response after you initiate therapy. When should one stop the therapy? You know, I think that, certainly, you know, the broadest response would be: when final height is reached. But I think that there probably should be careful observation of changes in height velocity, and determination of when the response to growth hormone is so low, in terms of a decrease in height velocity, that it no longer is reasonable to continue the growth hormone.

So, although I don't know what that number is, and it hasn't been defined, this is something that I hope will come out of a mandatory registry and follow-up type of study.

Then, number 2: the need for information on potentially useful predictors of response, both pre-treatment and on treatment; early growth or bio-marker effects, again, to enhance safe and effective use.

And I agree that we need to collect more information on these patients, although I wouldn't demand that that information be collected before

the drug was approved for more general use. I am a bit concerned that in this group of individuals with idiopathic short stature, non-growth hormone deficient short stature, that there's a group of individuals who have growth hormone resistence. And we need to be able to define those individuals, because it would be anticipated that those individuals would not respond to growth hormone, and we need to be able to define those, either by growth measurements, height velocity, IGF-1 response to growth hormone, or other parameters, and we're only going to be able to define that sub-group by doing those types of studies.

Dr. Cara?

DR. CARA: My answer to Question Number 3 is: yes. As a practicing pediatric endocrinologist, I don't think that we're going to see the thousands of patients that people have been concerned about. I think that my experience has been that, in general, parents are more interested in finding out if there's a problem or not, and are very willing to initiate therapy, but are also very relieved when their children are actually fine and don't need any treatment whatsoever.

Of course, to a large extent that's at the

discretion of the endocrinologist. But I trust most pediatric endocrinologists, being one myself.

So my answer to Question Number 3 is yes. 3.A--I think it's a good idea to have some criteria for initiation of therapy, and I think that the criteria that the sponsor provided is helpful--specifically in relationship to the degree of short stature, especially when we consider that the degree of short stature was probably one of the better predictors of ultimate response to growth hormone therapy.

3.B--are additional criteria needed? My answer is yes, but of course it's somewhat arbitrary, since we really don't have any idea of what pre-treatment criteria may ultimately define the response to growth hormone.

Personally, I would like to see IGF-1 levels in the less than 50th percentile range for age, which comes up to above the 50th percentile but no greater than the 90th percentile on therapy--or 97th percentile on therapy; appropriate treatment monitoring, in terms of safety issues. Keeping--again keeping the IGF in the upper end of normal but not exceeding the normal range I think is a good idea, especially when many of these

youngsters have low IGF-1 levels to begin with. I think using IGF as a criteria for pre-treatment and then efficacy of therapy is also very helpful.

It's helpful to have bone-age, chronological age and other serum markers, but I don't know that, other than height velocity, whether any of those other markers are truly helpful in making a decision. It's sort of the patient in toto that we have to be looking at, and not relying on a specific marker.

So, to summarize, I would recommend the height criteria that's been proposed by the sponsor. I would like to see an IGF-1 level below the 50th percentile for age, and a pre-treatment height velocity that's below the 50th percentile for age, as well.

3.C--I don't know that there is such a thing as individualization of dose when it comes to growth hormone therapy. We've generally tended to use the recommended dosages, .3 to .375 for most individuals. And I think that we've felt fairly comfortable doing so. Ideally, I would expect a response to growth hormone therapy of a minimum of 50 percent increase above basal growth rates, so that that might be a way that we can evaluate the

growth response. But I would be very hesitant about increasing doses further beyond the .37 dose recommendation. Again, I've commented before on lower doses, and I don't think that they are really work discussing any further.

3.C.2--again, having been in the growth field for quite a while, and having looked at a variety of predictors of response--and being frustrated at not finding any, I don't know that looking for potential predictors is really going to be entirely helpful. That said, I'm also not very comfortable with a notion of committing a child to seven to ten years of growth hormone treatment without having some sort of justification for it, or treatment efficacy that I can then use to say, yes, this is working, makes any sense either.

In my own view, I think an increase of 50 percent above basal baseline rate of growth is a useful indicator. And, again--well, having any additional markers, I think, is--well, it's going to be very difficult to determine those. That's the bottom line.

DR. BRAUNSTEIN: Dr. Tamborlane?

DR. TAMBORLANE: As far as the data as far as safe and effective use of Humatrope, I don't

know if this has come up yet. I certainly haven't heard it, but this issue about data about safety, I just want to follow up a little on that--is that, you know, there are, as far as I understand, literally thousands of youngsters who are classified as idiopathic short stature, non-growth hormone deficient short stature, that have been followed for years within the current registries--I mean, the Genentech registry and the other registries. So there is a tremendous amount of exposure. It's not just these 80 patients who were followed for a number of years. And nothing has certainly jumped out, to my knowledge, about safety. So, again, that's why I just want to fill in some of the--why I felt the safety profile was pretty good.

As far as--I thought the height criteria was reasonable. Remember, the height criteria--minus-2.25 is, you know, the cut line. And when you do that, then you come up with a mean of 2.7 standard deviations. So, I mean, I think that's a very reasonable way to try to limit the available population and that, you know, one of the safeguards as far as this floodgate sort of thing.

As far as additional criteria, I'd have to

think about this a little more, but I think that probably the one that I would be most in favor of is sort of an age criteria that the E001 when five years of age and up, so you have efficacy data in that age group. I think, as a pediatric endocrinologist, we know there's a lot of shifting of growth percentiles during the first two to three years of life. So I would hate to think that we would be treating a two-year-old who was more than .25 standard deviations below the mean. So I think a five year cutoff seems like a reasonable place as a starting point for discussion.

As far as IGF-1, you know we've heard, and it's been our experience, that none of these are great predictors. So that's what--I'd just go with age.

As far as what other trials--I think that the registry is very important. I think that we're only scratching the surface, as far as dose response characteristics. I think maybe--again, trying to add something to the discussion--what we may have if this is approved, in treating patients, and with the pivotal study showing proof of concept that it works, you may not--obviously, you have to go to final height. So you could do a series of

dose responses, and looking at different ages, and you may just need response over the first two years, and that might actually be your surrogate marker, rather than a biochemical surrogate marker to show relative efficacies of different dosing regimens at different ages.

DR. BRAUNSTEIN: Dr. Schade?

DR. SCHADE: Well, in answer to the first question, I'm concerned whether we have sufficient information to guide the safe and effective use of Humatrope. For example, since we're suddenly using it, or may be using it in large numbers, I have seen no data, for example, whether this drug is safe in a type-I diabetic. I have seen no data that this drug does not significantly augment insulin resistence in the obese child with a BMI greater than 35, and that's of great concern because, at least in my state, and probably throughout the U.S., childhood obesity has become an epidemic.

So, I'm concerned if you make a general statement, whether w e have the information available for safe and effective information on how to treat, I have no idea how to treat a type-I diabetic who happens to be in the short stature

category.

So, I think if we focus on certain populations that were in the clinical trials we may, but I didn't hear any data on two categories that I mentioned, and I could probably think of others. So I'm concerned about that first question.

And I think the height issue, I would agree that the company's recommendation is rational and statistically okay. And I really don't have any problem.

I'm also concerned--and I expressed it this morning, and I'm not arguing that it may not be difficult--but I'm very concerned that mechanistically we seem to have no way to predict who is going to respond, or whether the degree of response is proportional to some surrogate markers. And I didn't see any data on, for example, growth hormone levels after the injection. In many substances that we inject, different people characteristically have different responses. I didn't see any free fatty-acid data, which now has become a real problem relative to insulin resistence and causing insulin resistence.

I think we should look much more

thoroughly at finding surrogate markers, either relative to adverse events, or to response to growth. I think if we don't do that, if we say, "Well, we can't find anything," we'll end up treating many, many people with a huge degree of responsiveness, and that's of concern. Because I think what we ought to be doing is targeting the people who grow more than 1.5 inches. And if we simply say we can't do that, we'll never do that.

So, I'm a little concerned about the mechanism of responsiveness, that we haven't really had studies looking at that in any detail. And I would strongly recommend to the FDA that studies be initiated. I'm not saying hold up approval. That's not the issue. But I'm saying, when we're talking about treating up to 400,000 individuals, that if we don't have some handle on who's going to respond, we are going to be not only wasting a lot of resources, but basically causing a lot of children to take a lot of injections for no reason.

So I have some major concerns about all of these questions, and whether we really have adequate numbers--adequate amount of data to really guide the physician in using this drug in an intelligent manner.

I have problems with the concept of--quote--"letting the private physician or family make the ultimate decisions." They can do that, but they need the data, and they need the information on which to make those decisions, and I just don't believe we have them--or at least I haven't seen them presented today.

DR. BRAUNSTEIN: Dr. Woolf?

DR. WOOLF: What I'm about to say is probably heretical.

Yes, I agree with the height--that height restrictions should be there, but use of a 2.25 SD criteria is arbitrary. By definition of the pediatric societies, an SD below 2.0 is short stature.

If, in fact, short stature is associated with psycho-social issues, then 46 percent of the short children will not be eligible for treatment. So I would submit that if we're going to treat because there are issues, that we treat to an SD of 2.0, rather than 2.25. And that's probably heretical, at least from what we have heard today.

Now, I'm not saying that it is beneficial. That hasn't been proven. And I've said that before. But if it is beneficial, then roughly half

the children will not be eligible for treatment.

I would try to get as much information as possible on these kids. We're talking about having a mandatory or a near mandatory registry, and with only a couple hundred kids we may not have the information that we could have if we have thousands of children. So I'd like to get as much information as possible using the current state of the art--and I think the state of the art will jump light years ahead--and we've talked very briefly about this during a break, with DNA chips, and looking at responses and who are responsive, and what kind of path. And that may be down the road, not in the not too distant future. At least I hope it would be.

We have no evidence that going higher is better, and the .375 mg dose, I think, is certainly acceptable.

We don't know who will respond. Not everybody has response, and I would like to put a criteria on the continued use of the drug, that it will be discontinued if the response is less than x--and I don't know what x is--so that we don't have somebody take ten years' worth of treatment who will not respond--who does not appear to

respond substantially, but exposes them to whatever the risks of long-term treatment are.

DR. BRAUNSTEIN: Thank you.

Dr. Gelato?

DR. GELATO: Well, I believe that we do have evidence that can guide us to use the Humatrope in these children. I think that the height criterion--the way they've set it is fine. I'm actually comfortable with the fact that we're not going to be treating every short child, because I think we need to get some information, and maybe this will help us do it.

I think that we should have additional criteria. I think a pre-treatment height velocity would be important. And IGF-1 level would be other information, and the fact that the child has had provocative testing, I think, all should be collected. I'm not sure that it should necessarily be a criterion for therapy. But I do think we should get as much information as possible.

I don't know--I guess my feeling about individualizing the dose is that if you have a young child and you're treating them and all of a sudden you see that the IGF-1 level has jumped out of the normal range to something higher, then I

think, you know, one should cut back.

I think that there should be criteria in place for, if the is not responding--and I would certainly defer to Dr. Cara for what he suggested in terms of growth velocity--that the growth hormone should be discontinued. I think this will help us try to define who should be treated, what an adequate response may be, and maybe trying to define those people who have growth hormone resistence and may not be candidates for this.

I think, as Dr. Schade said, we should try to get as much information as we can on these children. If it's free fatty-acids, insulin resistence--whatever we can get--to try to help us better understand what the therapy maybe doing, and what some of the potential problems may be down the line. So I'm in favor of trying to collect what we can that's reasonable.

The other thing I"d like to say is that I also agree with an age restriction. And I probably would not treat children under the age of seven.

DR. BRAUNSTEIN: I'm sorry?

DR. GELATO: I would not treat children under the age of seven.

DR. BRAUNSTEIN: Okay--so we have "under

five," by Dr. Tamborlane; "under seven" by you--right? Okay.

Dr. Watts?

DR. WATTS: In all due respect to Dr. Tamborlane and to Dr. Grady's mother, I've been thinking about this issue of drugs to treat childhood obesity, and if the response was in weight loss what the response here is to height, I'm not sure the answer would be quite so easy. Because this is a change in height of 2 to 4 percent of adult height. And an agent that reduced weight in obese children by 2 to 4 percent, that had limited safety data might not be something to embrace.

DR. TAMBORLANE: I was afraid you'd figure that one out.

[Laughter.]

DR. WATTS: Yes. And if you're aware of registry data on thousands of children who've received growth hormone for this indication, that may reassure you, but I haven't heard anything about such data, and my comments and concerns about safety are limited to the information that I have heard here.

For 3.A, I think that this is an arbitrary

and logical height limitation, but if the real reason for treating short stature is because of psycho-social issues, it seems to me that it should be limited to short children who have psycho-social issues, and not just short children.

I don't know that I can tell you any additional criteria for treatment, other than a lower age limit--something along five to seven. But I think the studies listed here are studies that should be done as part of the work-up of a child who is going to be receiving growth hormone treatment.

Need for information on useful predictors--I've mentioned; that as an adult endocrinologist, my answer to the overall question, "Are the available data sufficient to guide the safe and effective uses?"--no. From what I've heard today, I'm not sure of the dose to use; I'm not sure which children to treat; I'm not sure what to monitor; and I'm not convinced of safety.

DR. BRAUNSTEIN: Dr. Worcester?

DR. WORCESTER: I didn't have very much to say, but answering the first one, in terms of height criteria--I certainly would not want the population that this would be marketed for to be

broadened at this stage, so I like the limitation.

In terms of additional criteria, I certainly hope the follow-up studies would help us answer this much more wisely in a pretty short time. But right now I don't what age to say, but I certainly would think there should be a minimum age at which the treatment would be started.

And then my response to the wide range of individual responses to the product would be that what we need is very good guidance for the families making decisions about this, so that there's very realistic expectations. And I think that's as important as looking at the next couple questions.

DR. BRAUNSTEIN: Thank you.

Dr. Goldstein, I've been informed that you can participate in the discussion. So, do you have any comments on these questions?

DR. GOLDSTEIN: I would have prepared, Dr. Braunstein, but not expecting to be called upon--we've heard--and everything I'd probably wanted to say has either become moot at this point, or has been said by others, so--

DR. BRAUNSTEIN: Great.

DR. GOLDSTEIN: --thank you.

DR. BRAUNSTEIN: Okay.

Dr. Follman?

DR. FOLLMAN: In answer to Question 3, I think the data are sufficient to guide the safe and effective use of Humatrope in these patients.

The criterion that the sponsor has suggested of minus-2.25 seems, you know, arbitrary to me but, you know, what wouldn't be, in a way? These are--this was used as the inclusion criterion in the pivotal study, and it's more restrictive than the inclusion criteria used in E001. So--you have to come up with some guidance, and they've proposed something, and I can't think of a reason why we should pick a different number.

In regards to 3.B, I think additional criteria would be useful. I'm not exactly sure what that would be. I had a concern I mentioned earlier about the stability of the standard deviation score, and so I don't--I wouldn't want a patient to be--to get this without some historical or some trajectory data on that person.

Then age restriction had also been proposed here, and I would--you know, that sounds good to me. I don't really know the area that well, but I would think additional criteria would be helpful.

In terms of individualization of dose, I think this is an extremely difficult thing to try and do for this condition and this kind of endpoint. If you're looking at something such as high blood pressure you can try and individualize the dose; you can evaluate rather quickly. Here what you're aiming for is probably height at 18 years, and so how can you individualize that dose based on outcomes from a person until you wait 18 years.

I think it's going to be difficult to do a trial, you know, in the future, to try and answer this question, to look at different doses for different subgroups. And so I think this is a very difficult issue.

In terms of predictors of response, I think that's also somewhat difficult, but one thing that's been suggest that sounds promising would be to look at the early response--say, over a year or two.

DR. GRADY: I just want to thank you for this opportunity to uphold my reputation.

I think that we don't have sufficient data to guide safe and effective use. I think that the height criterion is not nearly restrictive enough.

It basically uses a descriptive statistical descriptive term to define around about 1 percent of all children as having idiopathic short stature and potentially needing treatment for that.

I think that the additional restrictions the company has modeled depend only on the physician's discretion, and the discretion of an insurance company--which certainly could change over time to prevent what could be 400,000 or--400,000 children, to cut that number down to about 40,000.

I also think that this is a descriptive cutoff based on standard deviations. If we think of any other situation in which we do that, it's always correlated with some real outcome. You think of a t-score. Well, the reason we choose more negative than minus-2.5 t-scores for treatment of low bone density is because that's correlated with increased risk for fracture. And here we have no similar data on the correlation of this cutoff with any real outcome.

Certainly the response to growth hormone seems to be continuous over a wide range of short stature. So, I also think that we need more information to individualize this. It seems--the

one-size-fits-all seems inadequate to me. I certainly agree that we should have some age restriction, and I agree with, probably seven. I think we should also not--suggest that this treatment not be used for kids with constitutional growth delay, because it seems that those kids do catch up adequately on their own.

And I think that there should be criteria developed for stopping treatment in the course of one or two years if it seems ineffective. Continuing treatment that requires six, seven injections a week, and costs a whole lost of money just seems inappropriate for 10 years with no estimate of response.

[Pause.]

DR. BRAUNSTEIN: Oh--Dr. Schade, on Number 3, are the available data from the studies presented sufficient to guide the sage and effective use of Humatrope in patients with the syndrome--with non-growth hormone deficient short stature?

We just need a yes or no on that one?

DR. SCHADE: Ahh--I don't believe so.

DR. BRAUNSTEIN: Okay.

And, Dr. Woof? Yes or no?

DR. WOOLF: No.

DR. BRAUNSTEIN: Okay. Thank you.

Okay, the next two questions, we don't need to go around, but I'm going--since we've discussed a lot of these things--we will--I do want the committee to chime in on whether they have any comments concerning these.

The first one is: please comment on the sponsor's risk-management proposals.

And I'll remind you that what was presented is that to avoid inappropriate prescribing, they propose restrictive label; a specific description of appropriate patient population; physician education; limited marketing only to pediatric endocrinologists; no direct-to-consumer marketing; and a controlled distribution process.

In regards to the issues--the risk of lack of thorough diagnostic evaluation prior to initiation of treatment--again, the restrictive labeling proposal should take care of part of that. Physician education should take care of part of that. And the marketing to pediatric endocrinologists.

And then, finally, in regards to emergence

of new adverse events, they propose the post-marketing studies and the pharmacovigilance that they have in place for this.

Are there any comments from members of the committee regarding these?

Yes--Dr. Tamborlane?

DR. TAMBORLANE: I meant to ask this before, but--the issue about pediatric endocrinologists. You know, as you know, there's not enough pediatric endocrinologists, and there are major areas that are unserved by pediatric endocrinologists. So I assume you would not exclude adult endocrinologists who are taking care of children for growth disorders.

How does that work?

DR. QUIGLEY: That's correct. If you're in an area where the only population--where the population is served only by an adult endocrinologist, there are occasional, rare instances where we do qualify and allow those physicians to prescribe.

Could I also take the opportunity just to help to clarify something for Dr. Watts, while I have a second?

DR. BRAUNSTEIN: Yes.

DR. QUIGLEY: Because Dr. Watts, you indicted that you didn't--that we didn't present the data on the thousands of patients that have received treatment. And, in fact, maybe I didn't make it clear, but within the two current registries--the National Cooperative Growth Study, here in the United States, and the Kabi International Growth Study, which is global--there are close to 9,000 patients with this condition who've received treatment over the 15 years or so that these registries have been running, equating to approximately 300,000 years of patient exposures.

So I just wanted to be clear, because maybe I didn't make that clear in the presentation.

DR. BRAUNSTEIN: Dr. Worcester?

DR. WORCESTER: Yes, I wanted to comment on a couple things.

Of course, I was delight to see that there would not be direct-to-consumer advertising. But then hearing that there is a webpage actually scared me even more than direct-to-consumer advertising, in terms of how families with medical issues probably use the web information now, more than even watching television.

So if we're going to have a product like this, I would certainly hope the FDA would watch that website and make sure it was appropriate.

And then, of course, it won't be surprising to anybody that I'm also concerned about most of the medical education for physicians, which are going to play such a crucial role in terms of the gatekeepers for this being industry sponsored. I would certainly want to see a much wider range of medical education on such an important and controversial product.

DR. BRAUNSTEIN: And, to be fair, they do, in the booklet, indicate that they will sponsor, with unrestricted grants, CME programs for physicians.

Yes--Dr. Goldstein?

DR. GOLDSTEIN: I'm afraid a case of staircase wit, and I would now like to take advantage of your invitation to make one, I think important, comment.

I would urge that you not gauge this by age five, six or seven. There is--or anything like it. There is so much variability in children, and to do it by age is rather like prescribing by Young's rule, or Clark's rule, or things that went

out 40 years ago. Or, if you have surface area data available, prescribing in kilos or pounds.

It would be much better to select an objective criterion, such as SDS and the like, and settle on that--not age. Many, many five-year-olds that I've seen are bigger, or have different body characteristics, or have other disorders that make them look like an eight-year-old, much less a seven-year-old.

So, age is not where I would set my marker.

DR. BRAUNSTEIN: Okay.

Dr. Woolf?

DR. WOOLF: I have a question for the sponsor, and that has to be with vetting of the person who is permitted to write the prescription. Does it have to be a board certified endocrinologist? A board eligible endocrinologist? Somebody who practices pediatric endocrinology but who has never been specialized?

I mean, how do you restrict prescribing privileges, and who is the keeper of that key?

DR. QUIGLEY: Prescribers need to be endocrinologists--board certified. Mm-hmm.

DR. BRAUNSTEIN: Yes--Dr Cara?

DR. CARA: I just wanted to comment regarding the risk-management and additional concerns.

I think, as somebody that's been involved with growth hormone for awhile, I think growth hormone is probably one of the most scrutinized drugs currently available on the market. And I can understand a lot of the concerns that have been raised regarding the use of growth hormone.

That said, I can almost guarantee you that anybody--either parent or physician--that is interesting in getting growth hormone can probably now get it. So that the--I think this is a unique opportunity to be able to develop a program of not only treatment, but also monitoring to make sure that growth hormone is indeed used efficaciously, and used within appropriate clinical guidelines so that we do avoid the surreptitious use of the drug by--quote-unquote--"potential abusers."

So I would take this opportunity to put the sponsor within the responsibility of developing educational programs, perhaps even a web page--educational web page--for physicians or for patients that can be monitored by the FDA. I think those sorts of things are critical, but I think

especially the concept of being able to now monitor the actual treatment of these children who are now being managed haphazardly is something that really needs to be looked at.

DR. BRAUNSTEIN: Great.

Are there any other comments or concerns on the part of the committee regarding safety and efficacy that has not been already stated by the committee members?

Dr. Watts?

DR. WATTS: After Dr. Quigley's comments, I've looked back in my material, and I confess I can't interpret these data.

Slide 81 and 82 are the registry data, and one is expressed as "adverse events per 100,000 treatment years," which is a denominator I have trouble dealing with. And the other is "Even rates are reported as percent of total events," rather than percent of population. But it's looking to me like there's 13 percent diabetes, and other numbers that I have trouble--

DR. QUIGLEY: May I clarify for Dr. Watts? Yes.

In the Kabi International Growth Study, the event rates discussed here as rate per 100,000

treatment years because of the very low rate of events--of occurrence of events. So, as you can see here, this is 3.5 thousand patients with idiopathic short stature--their term for what we call non-growth hormone deficient short stature, compared with a similar number of patients with Turner's syndrome--substantially greater numbers than patients with chronic renal insufficiency, or small-for-gestational-age, two currently approved non-growth hormone deficient conditions.

So the information that we have from this global study is that the rates of adverse events in this patient population are similar to or lower than the other non-growth hormone deficient populations.

Can I have the next slide, please? The KIGS data. Sorry that's--oh, yes. Sorry. No, this is the right one. NCGS.

This is a little confusing to understand, and it's made further confusing because we've actually left off two columns from the original table, just to try to shrink the amount of data that was on the table. There is an additional column here of "organic growth hormone deficiency," and an addition column here of "other growth

disorders."

The key points to understanding it are that, again, to note that there is a substantial number of patients--5.5 thousand--compared with 3.5 thousand with Turner's syndrome, and just in the hundreds with chronic renal insufficiency. So substantially greater exposure in this patient population than the other two non-growth hormone deficient populations in this table.

The way the data are expressed is that this number here represents the percentage of patients within the patient database that this condition occupies. And then these--so these numbers, if you add in the other two columns, would add up to 100 percent across the row. They don't add up to a hundred percent because you don't have the other two columns. But what's obvious is that all of these numbers here, for all adverse events in the various sub-types are lower than the 17 percent that this patient groups represents within the total database.

Does that help clarify?

DR. WATTS: Not really What I'm interested in is how many children treated with growth hormone for this disorder develop diabetes, or scoliosis,

or--

DR. QUIGLEY: Develop--

DR. WATTS: --or slipped capital femoral epiphysis.

DR. QUIGLEY: The actual, absolute numbers.

DR. WATTS: The percentage.

DR. QUIGLEY: This is--

DR. WATTS: That's the percentage of adverse events that were diabetes, as I read the table.

DR. QUIGLEY: No. That's the percentage of the cases of diabetes that occurred within this patient population. There were actually only something in the order of--

DR. MacGILLIVRAY: 27.

DR. QUIGLEY: Yes.

DR. MacGILLIVRAY: 27 total out of 33,000.

DR. QUIGLEY: Right.

DR. MacGILLIVRAY: And of that 27 patients, 25 percent fell into the IGHD, and 8 percent fell into renal insufficiency. So it was percentage of the patients who got diabetes, and there was 27 type-I's.

DR. WATTS: What I'm interested in is how these patients do compared with the general

population, not how they do compared with chronic renal insufficiency.

DR. QUIGLEY: Okay.

DR. WATTS: And the way the data are displayed in this table and the previous one doesn't help me very much.

DR. QUIGLEY: So you're asking--

DR. WATTS: I get the sense that the numbers are very low--

DR. QUIGLEY: They're very low--

DR. WATTS: --but it's late in day and I'm calculator dependent, and I'm not sure.

DR. QUIGLEY: They're low, and they're no greater than the population base rate--for diabetes, at least.

DR. BRAUNSTEIN: Okay. So the last statement was: they're no greater than the population based anticipated--I mean, if you just look at patients with non-growth hormone deficient short stature not receiving growth hormone, they have the same risk of developing these things? Is that--

DR. QUIGLEY: The same risk as the general population; the general pediatric population or--in fact, lower--I mean, certainly no greater than the

general pediatric population, unselected for disease.

DR. BRAUNSTEIN: Okay. Thank you.

Any other questions about safety, efficacy?

[No response.]

Then we'll go on to the final question, and then I'll try to summarize what's been said.

Do you recommend that the use of growth hormone in non-growth hormone deficient short stature, as proposed by the sponsor, be approved by the FDA?

Dr. Cara, you start.

DR. CARA: Yes.

DR. TAMBORLANE: Yes.

DR. SCHADE: Ahh-yes, with the addition that the follow-up comments be included, that additional things need to be added relative to monitoring.

DR. BRAUNSTEIN: Dr. Woolf?

DR. WOOLF: Yes, provided that it's discontinued for non-responders.

DR. GELATO: Yes, with some of the additional criteria that we talked about: height velocity and age. And also that it be discontinued

if children are not responding appropriately--increase in height velocity.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: I think if these are the best data that you can get, then the answer is yes. But if you think you can get data on hard endpoints, then I think those data should be forthcoming, because the potential expenditure for this is considerable.

DR. BRAUNSTEIN: Dr. Worcester?

DR. WORCESTER: I'm voting no. I'm worried about the medicalization of shortness, and that it would actually increase the problem of the stigma.

DR. BRAUNSTEIN: Thank you.

DR. FOLLMAN: I vote yes.

DR. BRAUNSTEIN: Dr. Grady?

DR. GRADY: No.

DR. BRAUNSTEIN: And I vote yes.

Summary

DR. BRAUNSTEIN: So let me try to summarize the committee's responses. I'm probably not going to do it justice, but I'll try anyway.

Question Number 1: "Has the efficacy of Humatrope in non-growth hormone deficient short stature been sufficiently characterized?" The

answer was a uniform, unanimous "yes" on that.

"Is the dose-response regiment proposed supported by the results of the studies?" And the answer to that was "yes."

"Comment on the discussion by the sponsor of the importance of height augmentation in target population on the conclusion that the expected effects are clinically meaningful." And this is the area that had the greatest amount of discussion. It was pointed out that the studies that were performed--the pivotal study that was performed--probably underestimated the effect because older children were utilized.

One of the major problems is that there's no quality of life data that is sufficient for us to judge whether the clinical benefits of the height augmentation is really clinically significant.

The dose does appear to be okay. The majority of the group felt that the highest dose--the .37--was appropriate.

And, in regards to whether it is a clinically meaningful response, three members of the panel felt that the answer was "yes," and five had a very large question mark, and one felt that

the definition of "clinically meaningful" really must be defined by the patient and the family.

For Question Number 2: "Has the safety of Humatrope in non-growth hormone deficient short stature been sufficiently characterized?" Basically, there were three out of 10 of the committee who felt that it had not been sufficiently characterized in this group of patients.

"Do the results of the trials and the clinical knowledge of the safety profile of growth hormone in children support a favorable balance of risk and benefit?" And, again, because many members of the committee were unsure about the overall benefit in regards to quality of life, and whether it reduces some of the stress on short kids and short adults, as to whether there was a reasonable risk-benefit profile--but I think the majority of the committee felt that--felt fairly secure that the drug is reasonably safe.

"Please comment on the proposal for long-term follow-up of these children as part of the GeNeSIS system? What other surveillance of the safety of this intervention, if any, are recommended?" With one exception, nine members--well, nine

members of the committee said that a mandatory registry and follow-up of these patients be instituted. One individual felt that it should not be mandatory.

Question Number 3: "Are the available data from the studies presented sufficient to guide the safe and effective use of Humatrope in patients with non-growth hormone deficient short stature?" There were two members of the panel that did not feel that the data was sufficient. There were, by my count, four members of the panel that felt that it was sufficient; and one--there was a question mark.

"The sponsor has proposed a restrictive height criterion for treatment eligibility. Is this proposal satisfactorily rationalized?" Three members of the panel felt that it wasn't satisfactorily rationalized; that included one member who felt that if one is going to treat short stature, and short stature is defined by the learned societies--Pediatric Endocrine Society, for instance--as being less than 2 standard deviations below the mean, that that's the criterion that should be used. The other two felt that minus-2.25 was not sufficiently rationalized, and the other

seven members of the voting committee felt that it was.

"Are additional criteria needed, such as pre-treatment height velocity, bone-age, chronologic age, serum IGF-1 level?" And, here, the committee did not take a specific vote. One member of the committee suggested that requirements be, in addition to the height standard deviation being less than 2.25 standard deviations below the mean, that also the IGF values should be less than the 50th percentile, and the pre-treatment height velocity be less than the 50th percentile.

Others, including myself, felt that a variety of data should be collected on these patients, but that it does not--that information was not necessary to--as necessary criteria for institution of therapy; that therapy could be instituted based on the bone--based upon the height being less than 2.25 standard deviations below the mean. But the other information that was suggested included pre-treatment height velocity, bone-age, chronologic age, serum IGF-1 level, and provocative tests for growth hormone; and certainly that information should be compared to the information derived from the follow-up studies while the

patients are on treatment.

3.C--"The range of responses observed in the trials, and thus expected in the clinic, is broad. Additionally, a dose-response is evident. Please discuss the following: 1) the need for information on effective individualization of dose, age at initiation of therapy and duration of therapy, and growth response, and on safety." Several members of the committee felt that there should be an age limitation; that is an age below which growth hormone should not be initiated. One member of the committee felt that it should not be initiated for anybody less than five years; two members of the committee felt that age seven years was reasonable; and another member of the committee felt that a minimum age should be established, but wasn't quite sure what that should be.

Another criterion that was suggested was that during therapy the IGF-1 levels should be kept at the upper limit of normal. Two members of the committee felt that that was appropriate, but there was not vote taken on that particular issue.

How long should the therapy be given? One member of the committee felt that the therapy should be given for five years and no longer.

Another member of the committee felt that patients with constitutional growth delay should not be treated, especially if their predicted height is going to be sufficiently well into the normal range as to indicate that they'll eventually be normal-sized adults.

Under C.2--the need for information on potentially useful predictors of response, both pre-treatment an on treatment; early growth or biochemical effects, again, to enhance safe and effective use--the members of the committee that commented on this all said that, yes, we want predictors of response, we just don't know what they are; although one member said that there should be at least a 50 percent increase in growth during the first year for there to be considered to be a response.

Another member of the committee felt that therapy should be clearly discontinued if there is no response, but did not define what that response was.

In regards to sponsor's risk management proposals, they appear to be appropriate, with the caveats that the follow-up information be a mandatory requirement, and that this should be

easily instituted, since the distribution of growth hormone will be so tightly controlled to pediatric endocrinologists or endocrinologists taking care of short kids in underserved areas.

And then, finally, as far as a recommendation to the FDA on whether growth hormone should be approved for the use in non-growth hormone deficient short stature as proposed by the sponsors, there were eight members of the committee that felt that it should, and two members of the committee that voted no.

So, unless there are any other comments from the committee or Dr. Orloff--Dr. Orloff, do you want to have any closing comments?

DR. ORLOFF: Just to thank everyone for their time and efforts, and we'll proceed from here.

DR. BRAUNSTEIN: Great.

Well, thank you all for attending, and thank you to Lilly and to members of the committee, as well as to the public representatives.

[Whereupon, at 4:50 p.m., the meeting was adjourned.]

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