DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

Tuesday, September 30, 2003

8:30 a.m.

Hilton Hotel
The Ballrooms
620 Perry Parkway
Gaithersburg, Maryland

PARTICIPANTS

Linda C. Giudice, M.D., Ph.D., Chair
Shalini Jain, PA-C, M.B.A.

MEMBERS

Susan A. Crockett, M.D.
W. David Hager, M.D.
Nancy W. Dickey, M.D.
George A. Macones, M.D.
Joseph B. Stanford, M.D.
Scott S. Emerson, M.D., Ph.D.
Vivian Lewis, M.D.
Larry Lipshultz, M.D.
Valerie Montgomery Rice, M.D.

SPECIAL GOVERNMENT EMPLOYEE CONSULTANTS (Voting)

Robert G. Brzyski, M.D., Ph.D.
Adelina M. Emmi, M.D.
David L. Keefe, M.D.
Lawrence C. Layman, M.D.
James H. Liu, M.D.
James P. Toner, Jr., M.D., Ph.D.

ACTING CONSUMER REPRESENTATIVE

Lorraine J. Tulman, D.NSc.

FDA

Daniel Shames, M.D.
Shelley R. Slaughter, M.D., Ph.D.
Audrey Gassman, M.D
Kate Meaker, M.S.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. GIUDICE: Good morning. I am Linda Giudice and I am the Chair of the Advisory Committee.

Because we have new people in the audience today, I would like for the members of the Committee to please introduce themselves once again as we did yesterday, beginning with Dr. Hager.

Introduction of Committee

DR. HAGER: David Hager, University of Kentucky.

DR. CROCKETT: Susan Crockett, Christus Santa Rosa, San Antonio, Texas.

DR. MACONES: George Macones from the University of Pennsylvania.

DR. LEWIS: Vivian Lewis, University of Rochester.

DR. LAYMAN: Larry Layman, Medical College of Georgia.

DR. TULMAN: Lorraine Tulman, University of Pennsylvania, Consumer Representative.

DR. KEEFE: David Keefe, Women and Infants Hospital at Brown University.

DR. DICKEY: Nancy Dickey, Texas A & M

Health Science Center.

DR. GIUDICE: Linda Giudice from Stanford University.

MS. JAIN: Shalini Jain, Executive Secretary, FDA.

DR. LIU: James Liu from Case Western Reserve University.

DR. EMMI: Adelina Emmi from Medical College of Georgia.

DR. TONER: Jim Toner Atlanta Center for Reproductive Medicine.

DR. MONTGOMERY RICE: Valerie Montgomery Rice, Meharry Medical College.

MS. MEAKER: Kate Meaker, FDA.

DR. GASSMAN: Audrey Gassman, FDA.

DR. SLAUGHTER: Shelley Slaughter, FDA.

DR. SHAMES: Dan Shames, FDA.

DR. GIUDICE: Thank you.

As yesterday, we would appreciate it if your beepers and telephones would be put to vibrate or silent. I would like to begin the morning session by introducing Shalini Jain, who will talk about the conflict of interest.

Conflict of Interest Statement

MS. JAIN: Good morning and thank you for

your participation today. We are on a very tight schedule, so I will quickly read the Conflict of Interest, and I just wanted to let everyone know that we are flip-flopping the first and second presentations due to some presenter conflicts, so Dr. Layman will be going first instead of Dr. Liu, so there is a slight change in the timing of the presentations this morning, but we will have both speakers presenting.

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 present no potential for appearance of a conflict of interest at this meeting.

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 products they may wish to comment upon.

Thank you.

DR. GIUDICE: Thank you.

Issue: Discussion of NDA 21-322

Luveris (lutropin alfa for Injection)

Serono, Inc.

DR. GIUDICE: I would now like to introduce Dr. Lawrence Layman who is Chief of Reproductive Endocrinology, Infertility, and Genetics at the Medical College of Georgia in Augusta.

Genetics of Hypogonadotropic Hypogonadism in Women

DR. LAYMAN: Thank you. Good morning.

What I would like to do is go through what is known about the genetics of hypogonadotropic hypogonadism, which has been an area of interest of mine for a number of years.

[Slide.]

What I would like to do briefly is go

through normal pubertal milestones, the diagnosis of IHH, and then talk about the mutations with the prospective phenotypes for the hypothalamic genes that are known and for pituitary genes that are known.

[Slide.]

As everyone knows, GnRH in the hypothalamus stimulates the pituitary to make the gonadotropins FSH and LH, which then stimulate the gonads to make steroids and gametes.

[Slide.]

Typically, these result in females who have breast development and pubic hair development around age 8 to 9, their growth spurt is about age 12, and menses begin approximately age 12.

In males, testes and pubic hair begin at about ages 10 to 11 with penile growth about 13, and the growth spurt at about 14.

[Slide.]

What is often considered delayed is in females who have no breast development by 13 or no menses by 15, and in males who have no testicular enlargement by age 14.

[Slide.]

When hypogonadism is suspected, as

manifested by physical exam or low sex steroids, one of the steps is to obtain gonadotropins, and that helps classify where the defect is.

[Slide.]

If the gonadotropins are elevated in the presence of low sex steroids, the patient has hypergonadotropic hypogonadism or gonadal failure.

[Slide.]

Hypogonadotropic hypogonadism results when there is a hypothalamic or pituitary defect in which gonadotropins are low and sex steroids are low.

[Slide.]

IHH is often defined as irreversible absent puberty. In females, we usually use by age 17, who have amenorrhea, and usually, those patients don't have breast development. Males, it is generally age 18 with low testosterone. Gonadotropins are low or normal, and there is no CNS lesion by imaging, and there is normal prolactin, thyroid, and adrenal function.

[Slide.]

Gonadotropin responses are very variable to a single dose of exogenous GnRH, but Crowley's group, among others, have studied LH pulsatility

patterns including Dr. Santoro, who is here, and the most frequent pattern is the apulsatile LH pattern, however, decreased frequency and decreased amplitude have also been described, as well as a nocturnal LH prepubertal pattern.

[Slide.]

As we know, the prospects for fertility are very good with IHH. You generally induce secondary sex characteristics with sex steroids, the defect is hypothalamic or pituitary, and if there is other pituitary failure, those hormones need to be replaced.

For pregnancy, supplying the missing gonadotropins or GnRH gives excellent cycle fecundity rates.

[Slide.]

Looking at the genetics of this disorder, it is very complicated. I am only going to mainly speak about those in which IHH is the predominant feature, but just to be aware there are a number of syndromes in the on-line mendelian inheritance database.

[Slide.]

What I would like to do is first talk about the hypothalamic genes KAL1, FGFR1, and

NROB1. In addition, I will mention briefly leptin and the liptin receptor, and then talk about the pituitary genes for which there are mutations.

[Slide.]

The GnRH gene, now called GNRH1, is clearly a pivotal gene in reproduction and it is expressed in the hypothalamus among other places, and its deficiency should lead to hypogonadotropic hypogonadism since IHH is felt to be due to GnRH deficiency.

There is a deletion of GNRH1 in the mouse, however, none have ever been found in humans to date, so although this is highly likely to occur, one would think, none have been identified.

[Slide.]

Kallmann syndrome, which includes IHH plus anosmia, was the first disorder to have the gene identified. In addition, these patients can have neurologic abnormalities, such as synkinesia, which are mirror movements, visual abnormalities, renal anomalies, and midfacial defects, and in the original description, this was an X-linked recessive disease affecting males.

[Slide.]

It is known that GnRH and olfactory

neurons migrate from the olfactory placode to the hypothalamus, and two groups of investigators in 1991 cloned the gene by positional closing, and they identified it as KAL1, so that mutations in this gene result in anosmia and GnRH deficiency.

[Slide.]

In some of the original papers, when clear X-linked recessive families were studied, about 50 percent of these probands had mutations in KAL1, and very interestingly, of these, half of them had unilateral renal agenesis.

In looking at unselected Kallmann syndrome males, only about 5 percent or less had mutations.

[Slide.]

When expression was examined in both the chick and the human, the phenotype correlates nicely with the expression patterns. Certainly, the olfactory bulb with anosmia, some of the CNS defects, because of the cerebellum and spinal cord, and also renal anomalies correlating with renal agenesis, it is also expressed in facial mesenchyme, which does explain cleft palate, and cartilage and limb bud, which can explain an occasional club foot.

[Slide.]

Crowley's group has studied familial and sporadic Kallmann syndrome and has found in general about 12 percent of total Kallmann syndrome males will have mutations. Whether they are sporadic or familial, it is fairly similar. In normosmic IHH, none of 42 did in their study.

[Slide.]

This gene is on the pseudoautosomal region of the X chromosome with an inactive pseudogene on the long arm of the Y, and it encodes the protein anosmin-1, which is the protein that has neural cell adhesion molecules.

Orthologs have been identified in numerous other species including chicks, zebrafish, C. elegans, and Drosophila, but it hasn't been cloned yet in mice, but human antibodies detect it is present and at least as of last night, I didn't see it in Locus Link.

[Slide.]

The ortholog CeKall in C. elegans is required for ventral closure and tail formation in embryogenesis. It is involved in neurite branching, and it is also known that the human KAL1 cDNA can compensate for the loss of this, which suggests that this is a conserved function.

Anosmin-1 is a secreted molecule that binds via heparan sulfate proteoglycans to its receptor to induce axon branching and misrouting. This is in vitro.

[Slide.]

There are several possibilities of how Kallmann syndrome occurs. One is the absent lateral olfactory track branches cause anosmia, and the lack of GnRH neurons getting to the forebrain causes IHH.

It is also possible that anosmia could occur because of a lack of contact between olfactory axons and the olfactory bulb.

[Slide.]

Another disorder in which there are mutations is adrenal hypoplasia congenita and hypogonadotropic hypogonadism. Originally determined to be the DAX1 gene, it is now called NROB1, but these patients have adrenal failure in infancy usually to about age 10, and there are certainly exceptions, and if they survive, these patients get delayed puberty due to IHH.

It is X-linked recessive and mutations in NROB1 gene appear to cause both defects. It is expressed in the adrenal, hypothalamus, and

pituitary, and it's in the dosage-sensitive sex region on the short arm of the X chromosome.

[Slide.]

This is a study from Jamison's group suggesting that mutations have hypothalamic and pituitary defects. The double mutations shown at the top, one patient given exogenous GnRH had a normal response to GnRH suggesting a hypothalamic defect, however, with GnRH priming, had a minimal LH response suggesting pituitary effects.

Similarly, with a different mutation, there was no response to GnRH suggesting a pituitary defect.

[Slide.]

In collaboration with Jamison's group and Crowley's, we studied, John Achermann with Jamison studied about 100 IHH males without adrenal failure and sequenced the entire coding region and no mutations were identified, suggesting that it is very uncommon in IHH unless there is adrenal hypoplasia.

[Slide.]

There has been a mutation in a few females, one that is well documented, who had hypogonadotropic hypogonadism. She did not have

adrenal failure, but she had skewed X inactivation. Within that same family, there were two males who had hypogonadotropic hypogonadism and adrenal failure.

There is a female who has a missense mutation that was presented at the American Society of Human Genetics a year ago. This gene has been proposed to have some function in the ovary, but a study done by Jamison's group, a conditional knockout, demonstrated that there was not an ovarian determining gene, but is instead important in spermatogenesis.

[Slide.]

Several other hypothalamic hormones are important, as well. The leptin-deficient ob/ob mouse has a phenotype consisting of obesity, hyperinsulinemia, IHH, hypothermia, cold intolerance, and elevated cortisol.

[Slide.]

In humans now, there have been several mutations identified. Normally, there is a correlation between the BMI and leptin, and leptin deficiency is extremely uncommon in obesity. However, several mutations have been identified.

The first was an early onset obesity.

None of these families had any children of pubertal age, so this couldn't be examined, but in the second paper by Strobel, IHH and obesity were found due to a mutation, and the proband in this study was a male who weighed 55, with a BMI of 55.8, a low serum leptin, and he had a missense mutation in the leptin gene and had two sibs with similar phenotype, and this mutant in vitro was not secreted from the cell.

[Slide.]

Likewise in obesity and IHH with elevated levels of leptin, leptin receptor mutations have been identified, several, and in this one, cause protein truncation, and this also appears to be autosomal recessive.

[Slide.]

Very recently, a second mutation, a gene with mutations causing Kallmann's syndrome, which as we know occurs in males and females, and this group described mutations in an autosomal dominant form in the FGFR1 receptor. They also termed this KAL2.

It is interesting because gain of function mutations cause craniosynostosis disorder, Pfeiffer syndrome, and skeletal dysplasia, but these are

inactivating mutations.

[Slide.]

What they basically did was they found two patients who had contiguous gene deletion syndromes, who also had Kallmann's syndrome, and in that region there were only three genes - FGFR1 was the prime candidate and although by Southern blot there were no mutations, upon sequencing, about 9 percent of patients had mutations, and these were males and females.

Within these families, there is reduced penetrance and variable expressivity making it very difficult to follow.

Interestingly, some of these patients also had cleft lip and palate, synkinesis just like in X-linked recessive Kallmann's syndrome and dentogenesis.

[Slide.]

These investigators hypothesized could anosmin-1, the KAL1 protein, be the ligand for FGFR1, and there is circumstantial evidence for this, they did not study it in this study, but FGF interacts with its receptor via heparan sulfate proteoglycans, and so does anosmin-1.

In addition, KAL1 is expressed in

olfactory bulb in human, and in the mouse, FGFR1 is expressed in the forebrain and is necessary for olfactory bulb evagination, so circumstantial evidence supports this possibility.

[Slide.]

Now, moving to the pituitary, there were two papers that came out fairly simultaneously. A French group described a patient with incomplete pubertal development, incomplete IHH, and we found mutations in a patient with no pubertal development or complete IHH.

[Slide.]

The French group identified a male who had absent puberty at age 18. He was hypogonadal, his testosterone was 80 ng/dL, his gonadotropins were low. There was normal frequency of LH pulses, but decreased amplitude. Interestingly, he had a semen analysis of 39 million although only 5 percent motility.

[Slide.]

They found a mutation and then demonstrated the function in vitro. To do this, you have to look at several actions of GnRH. One is binding to its receptor, and the next is the signal transduction to IP3.

[Slide.]

This group identified two mutations. missense mutation that reduced binding and then subsequently, IP3 formation and efficiency, and the second missense mutation also reduced IP3.

[Slide.]

We hypothesized that since when you treat patients with GnRH, there is variable responses to GnRH that GnRH receptor mutations would be possible, and we screened 46 IHH patients using denaturing gradient gel electrophoresis, and we identified compound heterozygosity in one proband, one family.

Both of these mutations, actually one was the same the French group identified and another missense we identified, and both of them decreased receptor expression, binding was normal. The total IP3 was decreased, as well as the efficiency of IP3, so the EC50 was increased meaning it took an increased GnRH agonist to stimulate IP3 production.

[Slide.]

This is the family showing these patients, but what I want to point out is that the basal LH levels were low in all of them, and it will be easier to see on your handout. I apologize, this

is a little small.

But two of the patients had LH responses that got over 12, and the other two had ones that were about half that. So, there is phenotypic variability within the same family.

[Slide.]

The prevalence of GnRH receptor mutations is not entirely known. In our original study, there was 2 percent. If you included normosmic IHH with the female as a proband, it was 7 percent. Although they didn't allow us to include in the paper, we had originally screened 50 anosmics and did not find mutations.

[Slide.]

Crowley's group has studied approximately 50, and they identified mutations in about 10 percent. In the small number of autosomal recessive families, 2 of 5 had it, but again, in anosmic or hyposmic, they found no GnRH receptor mutations.

[Slide.]

At the Endocrine Society, we presented our data on 165 IHH patients studied, and this includes anosmic and hyposmic and euosmic patients. About 2 percent had mutations, and if there were two or

more affecteds in the family, it was about 7 percent, and about 5 percent if there were female probands.

[Slide.]

So, at least about 15 mutations have been identified. Most of these are compound heterozygotes and they may affect binding and/or signal transduction. The phenotype can vary from complete IHH with no evidence of pubertal development to partial IHH.

The patients to date don't have anosmia, and the gonadotropin responses to GnRH are very variable, in fact, there is even one pregnancy with multiple attempts of stimulating the GnRH, and the prevalence appears to be somewhere around 3 to 10 percent of normosmic IHH patients.

[Slide.]

Several other pituitary genes have also been identified that cause hypogonadotropic hypogonadism. It is known that an autosomal recessive form of combined pituitary deficiency, which causes a phenotype of short stature in IHH, has been due to a gene mutation called PROP1.

This gene is important in growth hormone prolactin, thyroid, and gonadotropins, and

occasionally ACTH is deficient. We screened IHH males and females who had no evidence of pituitary failure and found no mutations in this gene suggesting it is more common in patients with short stature and delayed puberty rather than just IHH.

[Slide.]

Another disorder of septo-optic dysplasia in which there is agenesis of the corpus callosum and panhypopituitarism along with some other CNS abnormalities may be due to mutations in HESX1, which is a homeobox gene expressed in Rathke's Pouch, which is the primordium of the pituitary, and autosomal dominant and recessive forms have been identified in some of these patients.

[Slide.]

In finishing with the gonadotropins, there are mutations in each of the gonadotropins. There are several polymorphisms that have been described in LH beta and there are two missense mutations on the same allele that are present in infertile and control patients, so they are probably polymorphisms, but it is interesting that they can interfere with the LH assay and that LH can be unmeasurable using an IRMA assay where you have a monoclonal antibody with the whole molecule and

measurable in an immunofluorescent antibody with two antibodies against LH beta.

[Slide.]

The only real true mutation that I have seen is one originally described by Axelrod, studied by Jamison's group, in which they had a male with delayed puberty, his testosterone is very low, and interestingly, his gonadotropins are elevated.

[Slide.]

When he was given testosterone, they were able to induce secondary sex characteristics, but even more interestingly, when they gave him hCG, it restored his adult phenotype and he got sperm. So, it suggested it was not an LH receptor mutation. This was long before the days of it being cloned.

[Slide.]

Jamison's group found homozygous LH beta missense mutation that was detected by dimer-specific IRMA assay, but it was undetectable by radio receptor assay, so they hypothesized that this mutant LH was not capable of receptor binding. This was an autosomal recessive inheritance with normal in heterozygotes.

[Slide.]

There have also been several FSH beta mutations in which the females have not had breast development, are in partial breast development (1), but all of them have presented with primary amenorrhea, they all have low FSH and high LH, and a low estradiol.

Their follicles do not go beyond the antral stage, and, of course, they have infertility, and the phenotype is similar in the knockout mouse.

[Slide.]

Interestingly, they have an elevated LH, however, they do not have hirsutism or hyperandrogenism, and some studies that I don't have time to go into suggest that maybe FSH is also necessary to make androgens in addition to LH.

[Slide.]

In males, there have been several mutations, as well. They have either had normal puberty or absent puberty where testosterone is either low or normal, but they likewise have a low FSH and high LH.

However, unlike the mouse, these patients uniformly have azoospermia, and we have not found mutations in oligospermic males.

[Slide.]

Similarly, it is possible, the similar argument that possibly FSH is necessary for androgen production, as well, which we are interested in testing.

[Slide.]

When these mutants are looked at in vitro, we have studied all of the FSH beta mutants and wild-type, as shown on the left, immuno and bioactive FSH was studied, and when we generated these mutants in Chinese hamster ovary cells in a vector, one provided by Larry Jamison, another one by a graduate student in my lab, we showed that none of them had any immunologic and biologic activity, probably interfering with dimer formation.

[Slide.]

In summary, hypogonadotropic hypogonadism, the genetics is still not really well worked out. There are no GnRH1 mutations, so if they are present, they are very uncommon.

KAL1 mutations appear to be present in about 10 to 15 percent of males. Interestingly, the KAL1 gene expression really explains some of the associated anomalies and may be useful in

clinical management.

FGFR1 mutations could occur in about 10 percent of males with Kallmann's syndrome.

NROB1 mutations have generally been found in patients who have adrenal failure and IHH, and otherwise, it is not common.

In the GnRH receptor, there are mutations in about 3 to 10 percent of patients, the phenotype is variable, and it can occur on males and females.

Rarely, leptin and leptin receptors cause mutations in obese IHH patients. That still leaves most causes of inherited IHH unknown.

Thank you.

DR. GIUDICE: Thank you, Dr. Layman. I understand that you need to leave. Do you have a couple of minutes for questions?

DR. LAYMAN: Yes.

DR. GIUDICE: Are there any questions by the committee members? Yes, Dr. Crockett.

DR. CROCKETT: Thank you for a very nice presentation, very informative.

I have one question about the FSH beta mutations that you mentioned. Am I to understand that this patient may present as a PCO-type-looking patient, but actually has some differences?

DR. LAYMAN: Actually, no, they are going to present with delayed puberty with absent breast development usually, maybe some breast development and primary amenorrhea, but they don't bleed the progestins, they are hypoestrogenic. Although the ovary is a little multicystic, which I didn't go into, on the patient we had, it is not a classical PCO-appearing ovary, but actually, multiple small cysts throughout the whole ovary.

DR. CROCKETT: Thank you.

DR. GIUDICE: Any other questions from the committee?

Okay. Thank you very much.

Our next speaker is Dr. James Liu who is from the Department of Reproductive Biology at Case Western Reserve University, and he is going to talk on Neuroendocrine Control of the Menstrual Cycle and Associated Disorders.

Neuroendocrine Control of the Menstrual Cycle and Associated Disorders

DR. LIU: Thank you very much. I was asked to discuss the basic neuroendocrine control of the menstrual cycle and focus and touch on some of the associated disorders that result in low gonadotropin states in which either GnRH or

gonadotropins would be amenable for ovulation induction.

[Slide.]

So, I am going to start at a very basic elementary level and work up. As we all know, and what Dr. Layman has originally presented, is that the changes with regards to estrogen, namely, puberty changes in the breast and the female habitus, as well as the menstrual cycle, is the end product of a coordinated series of events beginning with the higher neuronal centers that have input into the hypothalamus, which then modulates the gonadotropin-releasing hormone secretion, which is then interpreted by the pituitary as a neuronal signal resulting in release of LH and FSH, which then, in turn, drives the ovary to secrete estrogen and progesterone, stimulating the endometrium for appropriate preparations for pregnancy, and then failure to achieve a pregnancy, the ovary then has a timing mechanism in which the corpus luteum fails and menstrual flow occurs. That is really the final end product.

[Slide.]

Let's focus first on the hypothalamic pituitary compartment. In the normal individual

without gene defects, most of the GnRH neurons are localized in the arcuate nucleus, and they do migrate there from the olfactory bulb.

There are small nests of GnRH cells also in the anterior commissure and the OVLT, but, in general, most of the GnRH neurons are localized here. They have a coordinated network histologically, such that they can secrete the GnRH in concert, so that there is some linkage, which we don't currently understand, and it results in boluses of GnRH delivered to the portal circulation to the lateral wings of the anterior pituitary.

[Slide.]

If we look at trying to mimic the effects of GnRH peripherally and in a normal human intact model, here is an example of a very early study that was done by Dr. Yen's group, looking at IV versus sub-Q administration of GnRH in a peripheral sense to try and mimic the LH pulsatile activity.

These are GnRH, LH is in black and FSH is in the open circles, and you can see that there is a nice, very quick response within several minutes of exogenous GnRH in terms of response from the pituitary, whereas, if you give the GnRH in a sub-Q mode, there is atonic elevation of LH and atonic

elevation of FSH.

I will just briefly summarize it that sub-Q studies with exogenous GnRH were highly unsuccessful at inducing ovulation, and for the vast majority of clinicians that used GnRH for ovulation induction in patients with low gonadotropins, it was the intravenous mode.

With regards to the pituitary compartment now, we know that the pituitary and hypothalamus works as a unit in the intact human. It is very difficult to discern and separate out whether it's a hypothalamic versus a pituitary abnormality when we see low gonadotropins.

Systems that have been implicated based on animal studies in terms of regulating the secretion of GnRH are the opiate system, which the vast majority of studies would implicate a negative suppressive effect on GnRH secretion, the adrenergic system, the vast majority of animal studies would suggest an augmenting effect with regards to GnRH secretion.

The dopamine system is somewhat controversial. There have been some papers that have suggested that this augments GnRH secretion, there are some that suggest that it may actually

reduce GnRH secretion, so it is not clear, and the GABA system provides a negative suppressive effect on GnRH.

With regards to the pituitary itself, if you do staining on the lateral wings of the anterior pituitary, you will find that there are gonadotropes that contain LH-only, there are some that contain both LH and FSH, and some that contain FSH-only intermixed.

We now know that there is some paracrine regulation of FSH secretion in the sense of if the GnRH signal is a slow pulsatile signal, there is an increase in FSH beta message, as well as increase in FSH secretion. Within the pituitary are interstellar cells that secrete activin and follistatin. These two work in concert. One, activin enhances FSH beta message production, whereas follistatin decreases the FSH beta message.

So, the pituitary then, if you will, is an interpreter of the GnRH signal in terms of the amount of FSH and LH put out.

Now, we have taken advantage of the system in patients with low gonadotropins by artificially creating a pseudohypothalamus, and this is one of the orphan drugs that was approved by the FDA, the

Lutrepulse pump in which intravenous GnRH at doses of between about 5 micrograms every 60 to 120 minutes was capable of inducing a very characteristic physiologic response in terms of the LH pulsatile activity, and over a period of 14 days was able to stimulate normal follicular development and ovulation.

[Slide.]

Now, let's focus briefly on the ovary in terms of how the ovary interprets the gonadotropin message.

The basic follicle unit in the ovary is the granulosa theca cell unit, and the current understanding with regards to how steroids are produced by this in response to gonadotropins is based on the two-cell theory that was first proposed by Roy Greet [ph], but really Ken Ryan's group was the one that worked out the details in terms of how the system worked.

The theca cell, which is the red cells here, contain predominantly LH receptors, and it has the capability of cleaving the 27 carbon cholesterol to an androgen androstenedione by a series of enzymes under the direction of LH.

It is hypothesized that it serves as a

substrate which diffuses across the basement membrane, separating the theca from the granulosa cell compartment, and the granulosa cells, which contain initially FSH receptors, and as the maturation process of the granulosa cells in the follicle unit occurs, it begins to acquire LH receptors.

At the time of the pre-ovulatory surge, there is abundant LH receptors, such that when the trigger for ovulation, either hCG or LH increases, these granulosa cells can then luteinize and the ovulation sequence is induced.

The granulosa cell unit also is able to secrete inhibin, so it has two roles - conversion of predominantly androstenedione to estradiol because of aromatase activity. The FSH receptors are responsible for increasing the aromatase activity and conversion into estradiol.

So, both of these key things, production of estradiol and inhibin, serve to control the pituitary secretion of FSH.

So, to put the system together in terms of how it functions, pulsatile GnRH then drives pulsatile LH and FSH. The LH predominantly works initially on the theca unit to produce the

androstenedione, which then serves as a substrate under FSH stimulation, which induces aromatization of this androgen substrate by the granulosa cells.

Within the follicle unit on the basis of primarily rat studies, Greg Ericson and Erin Schwade being the principal individuals that looked at this particular model, the follicle that had the highest estrogen also had the highest number of FSH receptors, making the lead follicle much more sensitive to the FSH, because as the estradiol and inhibin are secreted into the peripheral circulation, pituitary FSH secretion is dampened, so that in a sense, the higher intrafollicular estradiol, higher FSH receptors within the granulosa cells promoted this particular follicle unit to continue to develop and the others to fade away.

Now, obviously, at the time of the LH surge, there is a trigger for ovulation, so what mounts this LH surge has been somewhat controversial although we now know that the hypothalamus and pituitary have the ability to integrate the estradiol signal, so that if the pituitary and hypothalamic unit are exposed to an estradiol level of about 300 for at least 60 hours,

it will spontaneously dump LH in the model.

This then triggers the ovulation sequence in the ovary approximately 36 hours to 40 hours later with ovulation.

With regards to what happens to the oocytes themselves, on the basis of studies by Gary Hodgins' group in the lower primate model, we now know that there is essentially a vast pool of primordial follicles in the young reproductive age woman, and this particular pool declines as the woman ages.

At some point, about two months prior to the onset of the menstrual cycle, a pool of follicles begin to undergo progression to an antrum form, and we don't know what controls this sequence of events from a non-committed primordial follicle to a committed follicle.

This is not gonadotropin-driven. The vast majority of these committed follicles undergo atresia. Of the few that go on, become gonadotropin-responsive and develop FSH and LH receptors, and in the absence of FSH and LH receptors, would undergo atresia.

As this pool of gonadotropin-responsive follicles begin to respond to the FSH, multiple

follicles can be seen in the ovarian stroma. The follicle that has the highest intrafollicular FSH receptors among the granulosa cells and the highest estradiol level will eventually continue to develop in the face of declining FSH due to the feedback effect of FSH and inhibin on the pituitary, and so this selects out a dominant follicle or what I call the "egg of the month."

So, this process of selection is important for the human, which is a mono-ovulatory species. Obviously, if we add gonadotropin at some critical level back here, we end up with multiple follicular development and rescue of follicles that would otherwise have undergone atresia, and this results in the multiple ovulations that we see in fertility and for in vitro fertilization.

[Slide.]

Now, we can follow this process also in the ovary. Here is an ultrasound of an ovarian cross-section with a black area, which is the fluid-filled ovarian cyst, and this particular cyst increases in size. This is the pre-ovulatory follicle.

The borders are less well seen in this photo because the patient had LH surge detected in

the urine, so there is already changes going on within the follicle itself, and after ovulation, the corpus luteum forms and there is hemorrhage and other changes within the follicle structure suggestive of corpus luteum cyst formation, and by day 25 or 26 of the cycle, this corpus luteum will be scheduled to undergo apoptosis, and then there is demise of the corpus luteum in the absence of pregnancy.

So, that is the normal menstrual cycle. So, what are some of the common programming that occurs in physiologic states? It turns out when the neuroendocrine axis reactivates, that it undergoes a very similar programming of essentially, if we look at peripheral LH levels being an indicator of endogenous GnRH secretion, since we have no way of sampling the GnRH compartment in the intact human, so assuming that there is a GnRH release for each LH pulse, we can make some suppositions as to what is going on centrally.

So, here is an individual who is in essentially a quiescent state. This would be individuals that are pre-pubertal or after delivery of a baby, when the HPO axis is essentially at

rest, or individuals with various forms of hypothalamic amenorrhea, which I will discuss.

As the GnRH axis activates, there are low amplitude LH pulses, so it starts off with a lot amplitude, low frequency pulses, and as the axis matures, and this can take place in a matter of weeks in the postpartum state, or in a matter of years in the pubertal state, there is an enhanced secretion of high-amplitude LH secretion during the sleep phase of the woman, and then during the early follicular phase, a normal pattern of well-established, about every 60 to 120 minute pulsatile release occurs.

[Slide.]

This is an actual example from Boyar's study looking at the GnRH-LH activation in puberty, and here are the sleep staging based on EEG criteria, and you can see the high amplitude up to 41 mIU of LH secreted during the state, and then during the daytime period when the child is awake, there is a much lower amplitude LH secretion suggesting that with sleep, some of the suppressive effects on GnR secretion may be decreased.

[Slide.]

This is a study I did many years ago that

looks at the same type of reactivation during the postpartum phase. These are women at various states after delivery day 19 though day 25, and you are looking at LH secretion. Primarily during the sleep hours, the LH is in black and the FSH is in open circles.

This individual is not breast-feeding, so prolactin levels return to normal levels pretty quickly and as you can see, there is a similar pattern to puberty of high amplitude, low frequency LH secretion with sleep, and then a maturing of that process by about day 25 following delivery.

[Slide.]

Now, I have just gone through some of the physiologic anovulation aspects, and we see that during the prepubertal phase, we also see it postpartum. This phase can be prolonged by breast-feeding due to the higher prolactin levels and the effects of prolactin on the hypothalamic pituitary axis.

But there are individuals that have a what we call "functional hypothalamic amenorrhea," and I will define that in generic terms in that if you do an evaluation of these individuals, they have no anatomic abnormalities, they have no gene

abnormalities, so these individuals may have a lifestyle-related shutdown of the hypothalamic pituitary unit.

These are individuals that may exercise excessively. A good example would be the long distance runner. When you classify them, and there have been studies that have looked at this, these are individuals that usually run more than 30 miles per week, they are relatively thin, and they are extremely committed to their exercise on a long-term basis.

There are individuals that have nutritional factors that affect their perception of body weight. An extreme form may be anorexia nervosa, a less extreme form may be bulimia, and there are individuals who are just plain stressed out from a variety of environmental changes, such as young girls going to college, having amenorrhea, or job stresses that may shut down the hypothalamic pituitary unit.

There are other disorders that are associated with medications, either individuals who are on a variety of antipsychotics which are predominantly dopamine receptor antagonists until recently where new, non-dopamine receptor drugs are

available, and there are extreme forms of psychiatrically associated disorders - pseudocyesis being an extreme form, and anorexia nervosa being the other, bulimia probably in an intermediate phase. I will discuss these in a little more detail.

[Slide.]

Let's talk first about the psychogenic hypothalamic amenorrhea. Individuals that have this particular trait usually are single, they are professional, highly intelligent individuals, that have sort of a Type A type personality, and many of them have obsessive-compulsive habits.

The history may pinpoint a significant stressful life event. It may be an onset of sexual abuse. Up to 20 percent of these individuals have this background history. They may also have a prior history of already an irregular menstrual cycle in that from the time of onset of menarche to when you are evaluating them, they have irregular menstrual cycles or very few menstrual cycles.

In general, they are involved in professional occupations just because of these particular traits that lend to success in professional settings.

[Slide.]

In terms of the hormonal parameters, Dr. Berga and I and other individuals in Dr. Yen's group have studied functional hypothalamic amenorrhea for a number of years and have published on some of the basis for the anovulation.

If we look at some baseline hormone levels, knowing full well that many of these hormones are secreted in a pulsatile fashion, and we compare them to the early follicular phase versus individuals who are amenorrheic on a functional basis, we find that the LH is lower, about 8.5 versus 11.6 mIUs. FSH is higher than LH in our laboratory measurements, so a reversal of the LH-FSH ratio that you might see in the adult.

Prolactin levels generally are a little lower perhaps related to the circulating estradiol levels, which can be lower, but not significantly, in this group of functional hypothalamic women. I will show you later on there are extreme forms, such as anorexia nervosa, where the estradiol levels are postmenopausal.

Cortisol secretion is increased over a 24-hour basis suggesting that the stress response has resulted in a much higher level of secretion of

a stress type hormone, cortisol. There is usually some decrease in T3. We didn't measure reverse T3, but I would suspect that reverse T3 would be somewhat elevated, and the T4 levels are somewhat decreased.

The yellow is the significant differences versus women that have regular menstrual cycles during the early follicular phase.

So, these are sort of the hormonal levels you might find.

[Slide.]

Here is an example of what we felt was an evaluation of the general overall stress picture. On this graph is the serum cortisol levels over a period of time as it begins to fall from early morning to the noon hours.

The dashed hatched area represents the normal levels of cortisol that we found in our control population, and these individual values represent the hypothalamic amenorrhea, and you can see with the exception of one individual, all of them have much higher circulating cortisol levels although they do all tend to have the same diurnal variation in terms of the decrease towards the noon hour.

If we look at LH secretion in particular with normal weight women versus hypothalamic women, the mean 24-hour LH levels are certainly lower, but not statistically significant, and they do overlap with normal women.

The amplitude of the LH secretion, based on pulsatile analysis, shows a higher amplitude LH in the hypothalamic women, about 8 mIUs mean in the hatch bars, however, what is most significant is the frequency is significantly decreased versus the normal weight women. So, this leads to an overall reduction in the average 24-hour LH secretion. This is for functional hypothalamic amenorrheic women.

[Slide.]

There are other abnormalities in our investigations that we found. This included, as I have alluded to, an increase in daytime cortisol secretion and a distortion of the melatonin secretion that normally occurs nocturnally, an increased amplitude, and increased melatonin secretion overall.

There is also an increase in nocturnal secretion of growth hormone, and in individuals in later publications, not from our group, there was

demonstration of elevation in corticotropin-releasing hormone levels in the CSF fluid, as well.

So, there are a variety of other neuroendocrine abnormalities that are associated, not just isolated, to the gonadotropins.

[Slide.]

A second disorder that can result in amenorrhea is bulimia, and these individuals are generally female, 90 to 95 percent. It is very high among high school and college students, about a 4.5 to 18 percent incidence, and this disorder is characterized by individuals that essentially consume very large quantities of food over a short period of time, followed by either food restriction or self-induced vomiting, or the use of laxatives to get rid of the food load.

[Slide.]

The features that we found were individuals generally had irregular menstrual cycles although the majority of them were not amenorrheic. Because of the self-induced vomiting, they did have effects of stomach acid on their teeth, they may also have irritation in the esophageal area due to the gastric acids.

There may have been electrolyte abnormalities due to the loss in stomach acid, as well as laxative abuse, and individuals may use various compounds like ipecac to increase their self-induced vomiting efficiencies.

[Slide.]

This individual, I think you all know is someone with extremely low LH and FSH and has anorexia nervosa, and is being studied.

[Slide.]

This is a psychosomatic disorder of a very severe nature, characterized by extreme weight loss of more than 25 percent below ideal body weight. There is essentially a body image distortion. These individuals believe that they are fatter than they truly are, and they have an intense fear of gaining weight.

The incidence varies depending upon centers reporting between 0.64 to 1 per 100,000, and the vast majority are female between the ages of 12 to 30. Of significance is this disorder has a mortality rate of at least 9 percent in some of the reported studies, so this is a very extreme example of a very serious illness with a high mortality rate in a very young population.

[Slide.]

If we look at anorexia nervosa--and this is a study that I did on one isolated patient who was amenorrheic--you can see that the LH levels are under 5 mIUs, probably between 2 to 3 mIUs, with really virtually no pulsatile pattern that you can discern.

We also simultaneously measured ACTH. The normal ACTH levels in our lab are between 10 and 15, and she does run into that range, however, there are higher levels of ACTH that are above that normal range.

In this individual, the cortisol secretion is tonically elevated with no diurnal variation over this 24-hour period of time, so she has lost her normal diurnal variation in terms of cortisol secretion.

[Slide.]

As with puberty and postpartum, recovery from anorexia nervosa follows that preprogrammed sleep-associated increase in LH secretion, and this is a study by Boyar looking at the reactivation during recovery from anorexia nervosa with again high amplitude LH secretion followed by a lower amplitude LH during the daytime hours.

[Slide.]

The behavioral features for anorexia nervosa include preoccupation with handling of food. These individuals will weigh their food, sometimes they will weigh their vomit, they will weigh their bowel movements, so there is very extreme abnormal behavior.

They oftentimes exercise bulimic behavior and extreme calorie counting. When one asks them what their waist is based on moving a pair of rings on a broomstick, they will oftentimes distort their waist measurements to a considerable degree.

They are very hyperactive in an effort to burn up the calories. In that one individual I studied, she was running up and down the stairs to the GCRC, which is nine floors, and she was doing it 30 or 40 times a day to try and increase calorie burn. They have total amenorrhea, as well as constipation.

[Slide.]

With regards to physical characteristics, they have coarse, dry skin. They have defects in thermal regulation with hypothermia. Heart rate is usually below 60. Because of electrolyte abnormalities, and this could be a fatal

complication, they can experience cardiac arrhythmias.

They have low bone mass and anemia, as well as low white counts, and their hepatic enzymes can become elevated with prolonged starvation.

[Slide.]

With regards to neuroendocrine abnormalities that have been described, I mentioned already the extremely low LH levels that I showed you in that example, both LH and FSH, and these would approach the same levels one would see with Kallmann syndrome or the isolated gonadotropin deficiency.

Their ACTH cortisol axis is impaired, and this may be in part due to the higher baseline activity in their cortisol dampening the feedback response. They have low prolactin levels, high reverse T3, low T3 levels, and decreased IGF-1 levels despite increased growth hormone levels.

So, these are very, very distorted in terms of what the normal relationships are in both the hypothalamic- pituitary-ovarian axis, as well as the hypothalamic-pituitary-adrenal axis.

[Slide.]

So, how do we put this aberrancy in GnRH

LH secretion into perspective with regards to what we have observed in individuals with functional hypothalamic amenorrhea, individuals with bulimia, and exercise-associated amenorrhea, which I haven't covered in great detail?

Our feeling is that there is probably environmental, physical, and personal stresses that have an increased effect on the endogenous CRH-ACTH-cortisol axis. In animal studies at least, this results in an increase in beta endorphin activity, which has a negative impact on GnRH neuronal secretion.

There may also be effects on the dopamine neurons although we are not quite sure, and this, in turn, then reduces the pulsatile activity of the GnRH neuronal system, dampening gonadotropin release, and our feeling is that this is a reversible process in these individuals as we remove or modify these life stresses.

[Slide.]

Just to reiterate this point, this is a group of individuals we studied with pituitary Cushing's disease versus a normal control. This is the LH secretion over a 24-hour period. Notice that in the Cushing's disease patient, the axis is

half of what it is on the normal control.

You can see that there are very few, if any, LH pulses during the day, and these are very low amplitude, less frequent pulses in this individual with excessive ACTH secretion. It's sort of an accident of nature with regards to high ACTH output.

[Slide.]

With regards to the organic defects that Dr. Layman has gone through with regards to genetics, he went through Kallmann's syndrome in great detail, isolated gonadotropin deficiency.

There are other organic defects that result in the same picture, and these are individuals with a variety of pituitary tumors that may destroy the gonadotropin-producing capacity of the pituitary gland, individuals that have some sort of infarction of the pituitary gland, such as Sheehan syndrome, which is a postpartum pituitary necrosis due to excessive bleeding with the delivery.

Individuals that have pituitary apoplexy, which is infarction of the pituitary usually associated with large macro adenomas. Individuals with empty sella syndrome, which is a misnomer in

that in this syndrome, there is a defect in the diaphragmatic drainage of CSF fluid, such that the CSF pressure is increased in the sella tursica, and the pituitary, on its stalk, just cantilevers up underneath the brain, so it is not in its normal location. In general, prolactin may be elevated in these individuals due to the impaired delivery of dopamine through the stalk.

Individuals that have HIV or TB may have an infection that affects that pituitary hypothalamic area. A variety of head traumas where there is abrupt acceleration of the head resulting in partial shearing of the pituitary stalk as the brain and the pituitary decelerate at different rates in head trauma, and obviously, post-radiation effects on the pituitary itself.

[Slide.]

Here is a clinical example of an individual with isolated gonadotropin deficiency. There is two females here and a male. Notice in this 17-year-old, she is quite tall. The bony epiphyses do not close due to the lack of sex steroid estrogen being produced, and so you can see that all three of these individuals have very long bones, and there is absence of breast development.

In this individual, there was some delay in pubic hair development, but generally, we don't see a delay in pubic hair development. Here is a male with the same type of diagnosis.

If we do close-ups of the breasts, they are usually Tanner Stage I, which means that there is very little breast tissue under the nipple due to the lack of estrogen production from the ovary, which is essentially at rest and unstimulated.

There is usually no delay in pubic hair development. This is Tanner Stage II or III. In this case, this is a Tanner Stage II since the pubic hair hasn't filled the entire lower escutcheon.

[Slide.]

With regards to the diagnosis of isolated gonadotropins deficiency, as Dr. Layman alluded to, pituitary functions except for LH and FSH are normal, they do not have any other organic defects.

Kallmann's syndrome, which is a version of this, is also associated with anosmia and midline defects.

These individuals, as I pointed on the picture, are tall, slender, with long limbs. The treatment long term for these individuals is to

induce puberty wit sex steroid hormone replacement. Individuals that require fertility would be treated either with pulsatile GnRH, if there is a center that does that, or injectable gonadotropins.

[Slide.]

With regards to the GnRH story, this is a series of patients studied from Bill Crowley's group looking at various doses of intravenous GnRH at 25 nanograms per kilo, 75 nanograms per kilo, and 100 nanograms per kilo, and this is their estrogen and progesterone profiles during a stimulated cycle.

As you can see, there are varying responses particularly with regards to the ovarian response to the gonadotropins that are generated from GnRH. All of them seem very similar although the progesterone production generally tends to increase a little bit more in the higher dose GnRH groups versus the 25 nanograms. Here, you can see some that have very low progesterone production during the luteal phase.

The optimum doses for GnRH administration has been established and they range at around 2.5 to 5.0 micrograms per pulse at about a 60- to 90-minute pulse per day.

With regards to the H-P-A axis, what I have shown you is that the activation of the H-P-A axis requires a program of GnRH pulsatile activity every 60 to 120 minutes. There is a sleep-associated rise in LH and FSH, and individuals with a slow wave GnRH will preferentially secrete FSH-beta initially, and this is seen in puberty and postpartum.

The reproductive dysfunctions I have discussed, which is resulting in reduction of endogenous GnRH secretion, are associated with either exogenous stressors, exercise events, or eating disorders with anorexia being an extreme form.

This results in an increased ACTH cortisol secretion and hyperactivation of this axis with a reduction in GnRH pulsatile activity.

Let me stop there and not go further.

DR. GIUDICE: Thank you, Dr. Liu, for this really comprehensive review.

I think you have clearly demonstrated the heterogeneity of hypothalamic amenorrhea. Between your talk and that of Dr. Layman, there are I think some sort of take-home messages I think we all need to be aware of, and that is that there are

individuals who have extremely low gonadotropins and those who have relatively low gonadotropins.

From some of the studies looking at the mutations in gonadotropins, you can have immunoreactive gonadotropins or circulating levels that are measurable, but still have bio-inactive gonadotropins.

Questions from the Committee

DR. GIUDICE: With this as a background, I would like to take the lead and just asking you a couple of questions.

One, can you talk briefly about low gonadotropins, and I think this is germane to the issue at hand today, and some of the assays that may have changed from the 1980s to now and what are low gonadotropins?

DR. LIU: Most of the slides that I showed you, that measured LH activity from Crowley, Dr. Boyar, and Yen's group, utilized a standard that is no longer available, which is the Second International Reference Standard that was put out by the NIH and was a urinary standard.

We were measuring essentially serum species. Subsequent to that, the WHO has put out other reference standards and, in fact, when you go

back and re-run those serums, the gonadotropins are much lower with the newer standards.

So, the numbers that we see, that I presented, are actually going to be lower if you use the newer assays and the newer WHO standards. That is my understanding. But I don't know the exact, I don't think anyone has worked out--anyone could care to comment--no one has worked out the translation between the old Second IRP Standards, which a lot of the research labs are using, versus the new commercial WHO Standards.

DR. GIUDICE: I have one other question and that is, the data that you showed on GnRH pulsatility in replacement of GnRH with the pump, the Lutrepulse was the commercial pump that was available, this is IV administration, I am wondering if you could just comment for the group about the availability of this and essentially either gonadotropin replacement or gonadotropin supplementation in the setting of low gonadotropins.

DR. LIU: There are only very small numbers of groups that have had a great deal of experience with intravenous GnRH, Nanette Santoro from Bill Crowley's group, myself, and Dr. Philip

Corey [ph] in Italy are some of the ones that come to mind that have done a fair number of GnRH cycles.

That particular approach works very well if you are very experienced, but if you are doing one or two cycles a year in the isolated individual with low gonadotropins, it is extremely difficult to keep the IV in place. As you saw, the sub-Q administration does not work well, if at all, and so when the IV infiltrates, what you end up with is essentially a sub-Q administration pattern.

So, a lot of times when we do see couples referred to us for IV GnRH, it is because they have had troubles with the IV access on a long-term basis, because it takes about 14 days to achieve a dominant follicle.

The other issue I think is the availability of the Lutrepulse. As far as I know, it is no longer being supported at least here in the United States. I don't know if Philip Corey has continued support in Europe, but it was manufactured by Ferring using the Ferring Cyclomat was the one originally, was the pulsatile pump.

DR. GIUDICE: Thank you.

Dr. Hager and then Dr. Keefe.

DR. HAGER: Dr. Liu, as a follow-up to Dr. Guidice's question, in partner to our considerations, what level of LH and/or FSH would you accept to differentiate FHA from IHH?

DR. LIU: I don't think that you can find an absolute level. In general, the functional hypothalamic amenorrhea women will have higher gonadotropin levels than IHH, but I think you will see some overlap, so, for example, the IHH less than 1.2 has been used in this particular trial. That is an appropriate cutoff.

For FHA, you will find some women at the same level, that mimics it, but most will be above that level. A level of 5, again, this is based on the new assay and not the old assay. The old assay, the mean was 8. something. In our particular study, I believe it was over 40 women with functional hypothalamic amenorrhea.

So, I don't know how to translate those numbers to the new one, but I would assume 5 would be an approximate level for those.

DR. GIUDICE: Dr. Keefe.

DR. KEEFE: I have two questions related to the nocturnal LH pulses that one sees physiologically, as well as with recrudescent to

the reproductive system and pathological states.

The first is I always see the LH secretion measured. What is happening with FSH, does it ever go up at all?

The second one is has anyone attempted to mimic that nocturnal LH when using the Lutrepulse? You can imagine, you know, you show that there is some disconnect between the growth hormone and IGF-1, and, of course, at night, there are elevations of growth hormone, so you can imagine physiologic rationale for why hitting with GnRH at night, at least during the early phase, might have some advantages. So, those are two related questions.

DR. LIU: With regards to FSH, it does increase, and let me show you that slide if I can find it.

It does increase, but not as dramatically as LH because the half-life is much longer for FSH. Here you can see the FSH go up, and here, it slowly increases, so you see both go up, but the FSH is much more minimal than the LH. It may be reflecting the pituitary secretory capacity. It is reading the signal, but it may not be able to manufacture the FSH as quickly and release it as

quickly as the LH, so that is number one.

What was the second question?

DR. KEEFE: The second was a biologic intervention, you know, if you intervene with gonadotropin or GnRH pulsing at night initially, do you gain any advantage?

DR. LIU: The answer is probably no, you don't gain any advantage. This is purely a physiologic program that I am pointing out, that this is what happens in the natural instance. Giving GnRH at night versus during the day probably has no bearing on the pituitary LH production provided you have already primed the pituitary sufficiently to get its stores of LH and FSH up.

DR. KEEFE: Has it been tested?

DR. LIU: It hasn't been tested.

DR. KEEFE: Because you could imagine if this growth hormone peaks at night, as well.

DR. LIU: Right, and growth hormone may have an augmenting effect, right, I understand, but it hasn't been tested. The problem is we don't have a good handle other than to say that you need about seven days of exogenous GnRH priming to get a more robust LH/FSH response.

DR. GIUDICE: Dr. Rice.

DR. RICE: Dr. Liu, this may not be a fair question to you, but Dr. Layman sort of alluded to this earlier, about data that suggested FSH is necessary to making androgens. Are you familiar with what data he was referring to?

DR. LIU: Could you repeat the question?

DR. RICE: He alluded in his talk that there is some data out there that suggests that FSH is necessary, may be necessary to make androgens. Do you know what data he was referring to?

DR. LIU: No, I don't. If we look at the women that have FSH receptor defects, there is a Finnish group of women with premature ovarian failure. They have normal FSH, actually, extremely high FSH levels, but don't respond at the ovarian level. They do make androgens, but the FSH receptor functionality is not totally ablated in those individuals, so I don't know if that answers your question. It is not a black and white issue.

DR. GIUDICE: Dr. Macones.

DR. MACONES: Dr. Liu, just in follow-up to Dr. Hager's question, you mentioned an LH cutoff of perhaps 5 to differentiate functional from idiopathic, from IHH, and it sounded like there is still going to be some overlap even with that

cutoff.

I was wondering if there are any clinical criteria or additional criteria that you could use to further refine that distinction between the two groups.

DR. LIU: We did not use gonadotropins as the criteria for classifying people with functional hypothalamic amenorrhea for those studies, and I don't think people have used it since then either.

It is primarily a stereotypic where they meet certain lifestyle criteria associated with amenorrhea, so amenorrhea really is the initial screening point, and then we went through to investigate whether there were any other organic causes for the amenorrhea.

When we found none, we then looked at the history to subclassify what other common features were in those individuals, so we did not use gonadotropin as our initial cutoff, and we looked at gonadotropins obviously as the cause of their amenorrhea, but not as the classifying criteria.

DR. GIUDICE: As a follow-up to that, for women who have functional hypothalamic amenorrhea where the gonadotropins, at least in the older assays, hovered around 8, and most of us wouldn't

be so shocked at the 5.

It is still clear, though, that they need gonadotropin supplementation, so there needs to be some additional amounts, and having a specific cutoff, I think, is perhaps desirable for trials, but clinically, in practice, there is such a range that it is often really not ignored, one just goes ahead and does the supplementation.

Any additional questions for Dr. Liu?

DR. LIU: Can I make one more comment?

DR. GIUDICE: I think so.

DR. LIU: What you are measuring really is a moving target because it's a pulsatile FSH and LH secretion, so if you happen to draw the blood sample at the peak, that may change, and if you draw it at the trough, it may change, so you have a huge--because the amplitudes are 4 to 8 mIUs, so you can have various time points on that curve when you draw the LH. That is why it is so hard to establish a clear gonadotropin threshold.

DR. GIUDICE: Yes, Dr. Crockett.

DR. CROCKETT: I just have a clarification question. Right now in patients with FHA, it is very common for us to treat their symptoms with oral contraceptives to replace the estrogen that

they don't have.

I am wondering if you remove the need to cause them to ovulate for pregnancy, is there other benefit to giving the LH or FSH, or could you comment on just the difference between substituting GnRH versus the pituitary level versus the end organ level?

DR. LIU: The physiologic replacement would be ultimately the best thing, however, we have no way of giving that decapeptide physiologically without either an IV mode or some other drug delivery means.

So giving the target tissue the steroid, which is what is the downstream event is the most appropriate, so for long-term replacement, I would treat these individuals very similar to what you might do for IHH.

DR. GIUDICE: Dr. Keefe and then Dr. Stanford.

DR. KEEFE: As you can figure out, we are trying to get at this issue of the diagnosis, the diagnostic criteria, even though there are not explicit criteria available.

In your clinical practice, when do you decide to give a trial of clomiphene citrate versus

exogenous gonadotropins for somebody is at the borderline range, what criteria do you use besides the gonadotropins, which you have pointed out are kind of tricky?

DR. LIU: I am a cheapskate, so because of cost issues, I always go with a challenge of low dose clomiphene citrate--and there is no clinical data published, I can say that upfront--I use a half a tablet of clomiphene citrate based on my knowledge base that in a low estrogen environment, clomiphene acts as an estrogen agonist, so I don't want to give a very high dose of clomiphene because it may end up suppressing.

So, I would use a low dose for one to two cycles to see if there is any response. If there is no response, then, I move to gonadotropins, so it's just a clinical trial.

DR. GIUDICE: Dr. Stanford.

DR. STANFORD: It seems like you mentioned a variability of baseline LH measurements. It seems like one way to address that might be to draw a level and then routinely draw another level 30 to 45 minutes later.

I am just wondering if that has been done and how that worked out.

DR. LIU: It has been proposed and I am sure it has been done for some studies, but I don't recall the levels that they got. There have been some protocols in which three serial samples and then they were pooled, and then you measured the pooled specimen.

DR. GIUDICE: Dr. Liu, I would like to get back to Dr. Keefe's question about your clomiphene challenge. Can you give us some idea of how frequently you actually have a positive response to that?

DR. LIU: In my experience, it is about 30 percent will respond to very low dose clomiphene citrate, and it is really truly not a clomiphene challenge as we use in routine IVF, so it's a very low dose, about a half-tablet for five days, and we just measure either follicular response or LH surge depending upon the individual's ability to measure.

DR. GIUDICE: And "follicular response," you mean size of follicles and estradiol level?

DR. LIU: Correct.

DR. GIUDICE: Thank you.

Any other additional questions? Dr. Keefe.

DR. KEEFE: Have you ever had occasion to

look at the ovaries of these patients that have severe hypothalamic amenorrhea? What stage, are they at the non-growing stage or are some committed?

DR. LIU: You will actually see antral follicles in them, but you will not see follicles probably above 7 millimeters if they are truly quiescent and their amenorrhea has been more than about six months, so the volume will be reduced compared to someone who is in the normal cycling category in the early follicular phase.

DR. GIUDICE: Any additional questions from the committee?

If not, I would like to thank Dr. Liu for his presentation and participation.

Before we go on, in our flurry to have Dr. Layman finish his talk before he had to leave, I actually inadvertently passed over Dr. Shames' opening remarks, so if you have any opening remarks, would you please share them with us now.

Opening Remarks

DR. SHAMES: I just had some brief remarks, first, to thank you for yesterday's session. I think we will find it very useful in formulating a guidance which hopefully will make

development of these drugs more efficient.

Secondly, since I find I am answering a lot of questions about process and regulations, I just wanted to very briefly give an overview of what is going on today, which is that we reviewed the application that you are all seeing, this particular NDA.

We reviewed the information and data from the trials that were presented and found that it did not provide, in our jargon, as will be explained, substantial evidence to be approved.

The Division found that it was not substantial evidence. When that happens, the sponsor is given the opportunity for various forms of appeal of our decision, and in this case, they can appeal above our level, to higher levels in the Center for Drugs, or they have the option of presenting their information to an advisory committee.

So, what is happening here is they are going to present their view of the information and we are going to present our view of the information, and then we are going to ask you for your input regarding that.

I just wanted to give a little background

about what exactly we are doing here today.

Thank you.

DR. GIUDICE: Thank you.

Committee Discussion

DR. GIUDICE: There was some discussion sort of post hoc yesterday by some of the committee members, and then this morning at breakfast, regarding some of the recommendations that we have made for the guidance document.

In particular is the issue--and I hate to raise this again, but since it has been very much under discussion--the issue of pregnancy as the outcome for gonadotropins and the issue of the indications.

Some committee members have expressed the desire to have a brief discussion this morning about this. The issue of pregnancy, just to cut to the chase, has to do with certainly that is the goal of gonadotropin therapy for infertility.

We, and many members of the committee, felt it important that this message be sent to the FDA that if there is no flexibility in outcome, and pregnancy becomes the gold standard, that the n that is required for most pharmaceutical trials is going to be so large, and the expense so high, that

we may actually end up with few, if any, trials at all, which of course would be counterproductive to the goals of the physicians and the patients.

So, I would like to devote maybe about five minutes to this discussion, and for those of you who bent my ear last night and this morning, I would invite you to please turn on your microphones and begin a brief set of comments.

Dr. Crockett.

DR. CROCKETT: I would just like to address this question to Dr. Shames. I was wondering if you could please, for the benefit of the committee, explain how the indications are decided, how your breakdown for the indications are done, and why it is important that it is done the way it is.

DR. SHAMES: Well, I can answer that in a general sense. First of all, the guidances are only recommendations as we have been saying here. The guidances are often general, there is a lot of wiggle room in the guidances, that is just the way they are.

These are not regulations or rules or legally binding. The purpose of these guidances is merely to increase the efficiency of the

development of the products, so that sponsors have some general idea of how to develop drugs in a general sense, for the bulk of the drugs, say, in this situation.

We always are aware that there are exceptions and especially when there are small populations, we understand. Small populations or outcomes that are very long, and we recognize that, so if there are small populations or outcomes that will be long or burdensome, we understand that we don't want to make the development so costly that it will be essentially impossible to develop the drug.

So, I think I am trying to assuage your fears of this in that what we asked for yesterday are sort of general guidelines, because we haven't done that really in a long period of time, certainly since Shelley and I have been here.

We do welcome exceptions. I mean we are flexible, you know, it's a flexible thing, because these are not set in stone, and they are not regulations, they are just merely recommendations that we give as guidances, and people can come before they even start developing the drugs and talk to us about exceptions.

As far as the indications, generally, it is best, it makes the most sense to formulate the trials, so that the endpoints for the trials correlate with the indications, but that can be changed also. I mean we can look at individual cases and have individual indications.

Part of the reason we try to make these standardized is because we have some obligation not to be arbitrary and capricious in a sense, which sponsors call "unfair." We try to be as standard as possible, so we are not accused of treating people or sponsors differently, so that is why we have to have some standardization in these situations.

DR. CROCKETT: I guess what I hear you saying is instead of having a general indication, say, for ovulation induction and augmentation, it's advantageous when they are acting with sponsors to have the indications broken down into more specific categories, because it offers them an opportunity to better target their research.

DR. SHAMES: As we discussed, we do have to take into account what is going on at the moment in the particular area, what the science is in the particular area, so that goes into what the

indications are also.

This can be altered, these guidances, even if we have a guidance that is not draft, is actually a final guidance, still, if the science changes, we can alter the indication at that point.

DR. GIUDICE: Dr. Stanford and then Dr. Keefe and Dr. Toner.

DR. STANFORD: It just seems to me that the indications ought to match the main outcome, and in this particular case, if the outcome is accepted of follicular development, which is another discussion, and if it is effective for that, which is another discussion, but if that were all the case, then, it seems to me the indication should not be for the induction of ovulation, but for the induction of follicular development.

I mean it should just reflect what the output was. That would be my take on it.

DR. GIUDICE: Thank you.

Dr. Keefe.

DR. KEEFE: We are kind of picking up where we left off yesterday. Both of the presentations that Jim and I made emphasized the disconnect between follicular development and outcome, that there are is so many factors that are

egg-specific, embryo-specific, and that to target the pregnancy outcome would compromise the development of novel drugs that may well be equally good and spur competition and open options that have other advantages, convenience, and other factors.

So, I think the proposal we left with was that we are recommending the indication be multifollicular development for pregnancy instead of and pregnancy, leaving that wiggle room overt and clear.

DR. GIUDICE: Dr. Toner.

DR. TONER: I think the issue is really one of trade-offs. Clearly, a pregnancy endpoint is closer to the desired goal of the therapy, but as a practical matter, we it would probably increase sample size for most studies about 10-fold, from 100 to 1,000.

The precedence has been in this country for sponsors to pay for such cycles of novel therapies, which in this country are typically $10,000 a crack. So, 10,000 times 1,000 is 10 million as a study, and I am not paying that bill, and I don't mean to be facetious, but in the end, our patients are paying that bill.

So, as one of the considerations here, I think you have to recognize that this will make drugs more expensive, and to the extent that you believe using the pregnancy endpoint is worth that extra cost, then, you stick with the pregnancy endpoint, but I think you have to at the same time admit that there is a cost to the patients for that endpoint.

DR. GIUDICE: Thank you.

Dr. Slaughter.

DR. SLAUGHTER: I just wanted to comment a little further what Dr. Shames and also Dr. Keefe have said. We take into consideration the clinical relevance of the indication. In other words, the indication should mean something clinically.

With respect to follicular development, I think Dr. Keefe has said we don't know what that means for pregnancy or there are some questions about the distal relevance to pregnancy, so therefore, if you use that as a surrogate, the ultimate outcome is to look for pregnancy, the surrogate or the reflection of the surrogate in the indication ought to have direct clinical relevance.

We do have some flexibility. I think we heard very clearly yesterday that you think there

should be some flexibility in the outcome or the indication of pregnancy as it relates to women with Group I.

So, I think as far as both Dr. Shames and I can persuade you, putting this in a guidance document is not law, there is some flexibility. We are able to look at some things on the case presented to us and make appropriate or relevant adjustments in the ultimate indication.

DR. GIUDICE: Thank you.

Dr. Emerson, Dr. Brzyski, and then Dr. Rice.

DR. EMERSON: I think that if we are going to invoke economics in this, we also should invoke the economic cost of approving a drug that is not really effective for what people want it for, and that you are paying for whether you like it or not, and that is a much greater economic cost to society than the cost of mounting a clinical trial where per-patient costs of $10,000 is really quite routine.

DR. GIUDICE: Dr. Brzyski.

DR. BRZYSKI: I was trying to think of examples from other situations to try and enlighten myself. I don't know if it is relevant, but I just

thought of the issue of say there is experience with fluoride self-limitation for increasing bone density, so if that is the indication, then, I think that could be approved to increase bone density, but when patients start getting prescribed fluoride and they have more osteoporotic fractures in that setting, then, is that a good thing?

Well, it did what it was supposed to do, it increased bone density, but clinically, it had a negative effect on the patient quality of care, and is that a situation that the FDA and that the committee would feel comfortable with setting a precedent for.

Now, I can't say, I mean there has not been any experience with ovulation induction drugs, for instance, that would make people ovulate or stimulate follicular development, but actually impair the opportunity for pregnancy, but you could imagine that those types of drugs could come along.

DR. GIUDICE: Thank you.

Dr. Rice and then Dr. Lewis.

DR. RICE: Yesterday, we were presented with some I think very clear evidence from our two presentations that showed us that follicular development does not lead to pregnancy in different

subgroups of patients, and there are several variables that impact that.

So, if we are trying to advance or improve our ability to assist patients with their end goal, and that is pregnancy, then, it would seem appropriate for us to re-evaluate the criteria under which we are approving medications that can go beyond follicular development, and that is to pregnancy, because we all know that when those patients come in to see us as clinicians, yes, they may be excited they develop a follicle, but what they really want to know if this is going to assist them in achieving their long-term goal, and that is pregnancy.

The second comment that I will make, and I hope this does not offend the committee members, but I think that we must be very careful about our subgroup conversations and that this is the forum in which to have conversations in which we discuss the issues that are relevant to making these guidelines to the committee--or the FDA, excuse me.

DR. GIUDICE: I think perhaps the reason there were subgroup conversations is because there was an element of uncertainty at the conclusion of yesterday, and I agree with you, it should have

been brought up in this forum, but I am glad that we are having this discussion today, so that there will not be subsequent subgroup conversations.

Dr. Lewis.

DR. LEWIS: Thank you. Yes, we did visit much of this terrain yesterday, but clearly, pregnancy is the bottom line, that is what the patients want, it is not follicular development, and if you have a sufficient sample size, I think issues about individual egg quality should be taken care of with randomization.

I would also remind the committee that these are all international companies producing these medications, they operate in a variety of countries where it may not be so expensive to run clinical trials, and clearly, the drugs are much cheaper in other countries. The reason for that--I mean there are a lot of reasons for that.

So, I do think our patients pay the cost if we approve ineffective drugs, and I think we ought to stick with pregnancy as the standard except as we agreed yesterday, in cases of Type 1 anovulation where it is rare and it's unrealistic to expect that we are going to get a large n to prove efficacy.

DR. GIUDICE: Dr. Hager.

DR. HAGER: It was my impression yesterday that a great deal of latitude was offered in our suggestions. I felt that it was very broad and reiterating the WHO-I category where follicular development was certainly an option for those studies.

But I just want to remind us that we also reviewed not only follicular genesis, but we reviewed ovulation, chemical pregnancy tests, progressing on to gestational sac with fetal heart motion, so I believe what we were saying was that in WHO-I category, the development of follicles is certainly a way to evaluate the efficacy of therapy, but there are steps higher related to ovulation that would fall into that same category, that what we are really looking at for an ultimate endpoint in the other categories, assisted reproductive technologies, is a gestational sac with fetal heart motion.

DR. GIUDICE: Thank you. I am assuming there are no more hands, that everyone has gotten whatever they have had on their chests now off their chests.

Dr. Emmi, you have one more comment.

DR. EMMI: I believe that when everybody leaves the table with a little bit of thought about what they felt should have happened, it usually means that you have compromised, and I feel that the clinical pregnancy rate was a compromise amongst the two groups for the appropriate endpoint, which is actually pregnancy.

DR. GIUDICE: Thank you.

We are running a little ahead of time, so what we would like to do is take break now and return at 10:30, so the sponsor can begin their presentation at 10:30. Thank you.

[Break.]

DR. GIUDICE: The next series of presentations will be the sponsor presentation by Serono, Inc.

The first speaker is Pamela Williamson Joyce, who is the Vice President of Regulatory Affairs and Quality Assurance in Serono in the United States.

Her topic is Introduction and Regulatory History.

Sponsor Presentations (Serono, Inc.)

Introduction and Regulatory History

MS. WILLIAMSON JOYCE: Good morning. My

name is Pamela Williamson Joyce and I am Vice President of Regulatory Affairs and Quality Assurance for Serono.

I would like to thank Dr. Guidice and the members of the Advisory Committee, as well as the members of the Food and Drug Administration, for the opportunity to be here today to share the clinical development results for our program in Luveris, a recombinant luteinizing hormone.

[Slide.]

The proposed indication for Luveris is as follows. Luveris (lutropin alfa for injection) administered with follitropin alfa for injection, is indicated for the stimulation of follicular development in infertile hypogonadotropic hypogonadal women with a profound LH deficiency as defined by a level of LH of less than 1.2 IU/L.

Given the earlier discussion, I would like to take this opportunity to clarify the indication. In August of 2003, Serono proceeded to submit an amendment. We thought this might be good for two reasons.

First of all, this indication is consistent with the clinical development program over the last 10 years in studying LH and

stimulation of follicular development. Additionally, it is important to note that this is also consistent with the indication that is currently approved in 46 other countries outside of the United States.

[Slide.]

A brief overview of our presentation follows. After my introduction and overview of the regulatory history, I will invite Dr. Jerome Strauss from the University of Pennsylvania to speak on the need for and the rule of LH in HH women with a profound gonadotropin deficiency.

Following Dr. Strauss, Dr. Paul Lammers, Chief Medical Officer for Serono, will share the clinical development results in terms of efficacy and safety of Luveris.

Following Dr. Lammers, Dr. Nanette Santoro from Albert Einstein College of Medicine in New York will present the clinical perspective and benefit/risk of luteinizing hormone in these women.

Finally, I will conclude the presentation.

[Slide.]

Luveris is a luteinizing hormone produced by recombinant DNA technology. It is presented in lyophilized 75 IU vials and can be

self-administered by subcutaneous injection.

[Slide.]

Luveris is currently approved in 46 countries outside of the United States including the European Union.

[Slide.]

It is important to note for several reasons that FDA's Office of Orphan Product Development has designated Luveris to be an orphan drug. Specifically, in the United States, the orphan drug regulations provide incentives to sponsors for the development of drugs which are intended to treat rare diseases and conditions.

In the United States, that is defined by a prevalence of less than 200,000 patients. In this case, the prevalence of hypogonadotropic hypogonadal women is estimated to be between 2,800 and 5,600 women.

Furthermore, in terms of profound LH deficient patients, the number of women is indeed even smaller. This further points to the challenges in developing drugs for rare conditions.

[Slide.]

Back in the early 1990s, Serono recognized that for many women, FSH alone was sufficient in

their gonadotropin treatment regimen, however, we also believed that there was a role for LH specifically in the hypogonadotropic hypogonadal population. Therefore, we requested a meeting with the Food and Drug Administration--this was a pre-IND meeting--in order to seek advice on a clinical development program of using luteinizing hormone in treatment of HH women.

The clinical development program was agreed to be two, Phase II/III studies that were intended to be essentially the same in clinical design. The endpoint for those studies in terms of registration was agreed to be follicular development.

The first study, Study 6253, was conducted in Europe and Israel. This study, as Dr. Lammers will share, was of the truly profoundly LH-deficient patient population.

Study 6905, which was conducted in the United States, and also therefore filed to the IND, was intend to reflect essentially the same patient population, however, given the rarity of the condition, it was difficult to enroll and therefore a decision was made to broaden the inclusion criteria for the U.S. Study.

In hindsight, this was not the best decision because in the end, therefore, the population studied in the two clinical trials were no longer the same.

In March of 1999, both clinical trials were completed and the data were shared with the Food and Drug Administration, who at that time had pointed out that given the fact that the two patient populations were no longer identical, they would like us to perform a confirmatory Phase III trial.

This confirmatory Phase III trial was our Study 21008, which will serve as the basis of registration, and Dr. Lammers will share that with you.

It is important to note that there were a considerable amount of discussions during the time that we presented the initial data and then, therefore, agreed to conduct that Phase III trial.

Following completion of the trial, we requested another meeting with the FDA, and we met with the Division in December of 2000. This was a pre-NDA meeting where the results of the safety and efficacy of Luveris were shared.

At that point in time, there were no

concerns expressed to us by the Division and, in fact, a comment was made that we had indeed conducted the trial as had been requested, and that would be viewed favorably.

Given that, we proceeded to submit the NDA in April of 2001.

[Slide.]

In March of 2002, we received a Not Approvable letter, which indicated that we had not provided sufficient evidence to support the efficacy of the 75 IU/day dose, and the Division had requested that we conduct another Phase III confirmatory trial.

In this instance, the request was that the trial again be efficacy versus placebo, as in the previous trial, that the indication be for ovulation induction using P4, and that this also be a dose-ranging study which would include a placebo arm, the proposed 75 IU/day dose, and another dose, lower dose, either 50 or 25 IU/day.

Following the receipt of the Not Approvable letter, Serono requested a Type A meeting in order to hear from the agency the concerns with regard to approvability, and one of the concerns which we will speak to today, although

prospectively defined in the protocol, was told the fact that cycle cancellation due to risk of OHSS should be considered an efficacy failure.

In January of 2003, we met with the agency again to talk about what possibilities there were for us to provide any additional information to help clarify the concerns. At that point in time, the Division agreed and we agreed, mutually agreed that it would be prudent to bring the information for Luveris before an Advisory Committee.

[Slide.]

One thing I would like to take note of, which happened subsequent to the review, is that in April of 2003, as discussed with the agency, we amended our NDA to include additional results from an extension study.

The extension study, 21415, was a follow-on to the original pivotal trial, and this was intended to provide an additional three cycles of treatment to patients in order to allow them the opportunity to become pregnant and to gather additional data in terms of safety, efficacy, and pregnancy.

[Slide.]

A few of the topics that we would like you

to consider in your discussions today.

Is there a need for recombinant luteinizing hormone? We believe that some of the speakers that presented yesterday, as well as speakers that will present in just a moment, will clearly indicate that there indeed is a need for recombinant luteinizing hormone in treatment of these patients.

Has the appropriate patient population been defined? Some initial discussion has taken place earlier today on that.

Has a safe and effective dose been identified? Specifically, the 75 IU/day dose. Dr. Lammers will share that we indeed believe that the 75 IU/day dose is the effective and appropriate dose for these patients.

Is the composite primary endpoint of follicular development an appropriate endpoint to assess efficacy in this specific patient population?

[Slide.]

Further, to consideration of the efficacy endpoint, again, how should one consider in terms of analyses cancellation of cycles and also pregnancy?

Finally, do the data that will be shared with you today in terms of safety and efficacy support Luveris to be approved in this proposed indication, and should another Phase III, double-blind placebo-controlled clinical trial be required in order to grant approval of Luveris?

Certainly, although not first and foremost in these considerations, it is important to note specifically with regard to this patient, given the rarity of the condition and the amount of time that each of our previous clinical trials have taken to conduct, that we would estimate that to do a trial as requested, using ovulation rates and the three arms double-blinded, placebo-controlled, is estimated to take an additional 195 patients.

We estimate it would take at least five years to complete that trial.

[Slide.]

As I close, I would like to share with you the names of some of our external consultants who are here with us today. Although some of those folks may not be speaking, they are available to respond to questions that you may have.

First, Dr. Sarah Berga from Emory University School of Medicine. Michael Diamond

from Wayne State University in Detroit, Michigan. Dr. Gary Koch, who is our statistical consultant.

[Slide.]

Dr. Bert Spilker. Dr. Bert Spilker is co-founder and former President of Orphan Medical, and has extensive experience in the development and commercialization of drugs intended to treat rare conditions and diseases.

Dr. Nanette Santoro, Professor and Director, Division of Reproductive Endocrinology at Albert Einstein College of Medicine.

Jerome Strauss from the University of Pennsylvania.

I would also like to take this opportunity to note that both Drs. Berga and Santoro were clinical investigators during our clinical development program for Luveris. Both have extensive experience in treatment of HH women including those who are profoundly LH deficient.

With that, I would like to invite Dr. Strauss.

Need for and Role of LH in HH Women with Profound Gonadotropin Deficiency

DR. STRAUSS: Thank you.

We heard two excellent presentations this

morning that are relevant to the issue of the patient population for which the sponsor is seeking approval of its drug, and I would like to share some additional thoughts regarding the role of LH in follicular development and why it is needed in the treatment of infertility with women who have profound gonadotropin deficiency.

[Slide.]

I want to touch on the heterogeneity, the pathophysiology of this disorder, and the significance of that to clinical management, the consequences of profound LH deficiency, briefly on our current therapeutic options, and then some comments on the unmet medical need.

[Slide.]

As we heard this morning, HH can be caused by disorders in the central nervous system, hypothalamus, pituitary, or both the hypothalamus and the pituitary gland.

[Slide.]

It was mentioned that this is a very rare disorder and it's heterogeneous. Let me share a vignette with you that relates to the rarity of the condition.

The University of Pennsylvania was a

participant in the sponsor's confirmatory trial 21008. We have nine reproductive endocrinologists on staff who have 18- to 20,000 patient contacts per year, and even with that volume, we were only able to identify a single patient to participate in that trial. It basically says these individuals are as rare as hen's teeth.

I would also like to point that Dr. Layman, in his excellent discussion of HH, didn't specifically point out that there is a significant sex difference in the occurrence of this disorder. He talked about some significant numbers of patients, but you have to recognize that HH is five times more common in males than females.

Heterogeneity was touched upon by the two previous speakers, and that is important with respect to clinical management. It can span from pan-hypopituitarism, and those individuals may require gonadotropins and additional treatment, such as growth hormone, to achieve follicular development and to pregnancy.

There is the isolated severe gonadotropin deficiency, which we are going to discuss a little bit later in greater detail, and moderate impairment, which may be treated with, for example,

FSH alone.

But it is the severe gonadotropin-deficient patient which is the topic of today.

[Slide.]

How do we identify these patients? That has been touched on earlier. First of all, we have to recognize that these patients have very low gonadotropin levels, low FSH, very low LH, and they are also chronically hypoestrogenemic.

So, to capture the diagnosis, we have to use clinical judgment and oftentimes the history and physical examination is terribly informative, but there are some biochemical and functional tests that can be used to identify the patients who will indeed benefit from LH in addition to FSH in their therapy.

One mechanism to do that is to measure LH, and as was mentioned earlier today, an LH level of less than 1.2 IU/liter it a very reasonable index of the patients who will require LH in their treatment. That comes from literature.

One citation, which was in your briefing document from Shoham et al., demonstrated that patients whose LH levels are 1.2 IU/liter or less

do benefit from the addition of an LH activity in their follicular development stimulation protocol.

There are other papers with smaller numbers of patients that also confirm this, and indeed the sponsor has used that cutoff value in their clinical trials and confirmed the value of LH, as they will show you, in that patient population with that LH level.

I should also point out that these different studies that I have just mentioned relied upon different LH assays, so there is some robustness in the cutoff value.

The hypoestrogenemia can be identified by an endocrine measurement, and I would suggest an estradiol level of less than 30 picograms/ml, or a functional test, the progestin withdrawal test, and Dr. Montgomery Rice appropriately pointed out that that functional test has some warts, particularly when it is used as a primary diagnostic criteria, for example, the old WHO group I definition, but in the context of a patient with low LH levels, it does document chronic hypoestrogenemic state.

Now, I don't think this is news to anyone in this room who practices reproductive endocrinology, indeed, if we look at the ASRM

Technical Bulletin on Follicular Development and Ovulation Induction, it is recommended that patients with low gonadotropin levels be treated with a preparation that contains LH activity.

I should point out that the citation that is used to support that suggestion was a paper that I wrote with Michael Steinkampf [ph], and at the time when that paper was written, we were basing that concept recommendation on experience and the existing clinical literature at the time, because there were no randomized, placebo-controlled trials to establish that point.

As you will hear today, we now have that information which does indicate that in those individuals who are severely gonadotropin deficient, the addition of LH is indeed beneficial.

[Slide.]

Now, what are the consequences of profound LH deficiency, why is LH needed? To answer that question, we have to address, first, what are the roles of LH in follicular development, follicular function.

As Dr. Liu mentioned to you, LH is important for stimulating follicular steroidogenesis. It promotes the production of

androgens, which are then aromatized in the granulosa cells to estradiol, and that estradiol has important effects, not only on the central nervous system, as we heard today, it is critical for programming the reproductive tract, and that is important because you need to have an appropriately developed endometrium if you are going to achieve a pregnancy.

LH also synergizes with FSH in follicular development, as was mentioned, and indeed it can support the terminal differentiation of the follicle even in the absence of FSH. FSH is the main driver, but LH is clearly synergistic.

LH also promoted ovulation, which involves several steps. It is the resumption of meiosis, the actual release of the egg, and, of course, luteinization of the granulosa cells and the theca cells in the formation of a corpus luteum, and LH is necessary for the maintenance of corpus luteum function.

[Slide.]

Now, in thinking about endpoints for assessing the action of LH, one would like to capture all of the activities of LH in the follicular development process, and indeed

clinically that is done. We measure estradiol levels, an assessment of the steroidogenic activity, we monitor follicular growth by ultrasound, and we assess progesterone as an index of ovulation.

I should point out, however, that in the HH population that is severely gonadotropin deficient, exogenous progesterone is clinically, usually administered soon after the administration of hCG because those individuals will not be able to sustain appropriate luteal phase progesterone levels in the absence of either some gonadotropic factor or exogenous progesterone.

[Slide.]

Let me just briefly go over some of the important roles of LH and follicular function. Jim Liu showed us this, that LH acts on theca cells to stimulate androgen production, androstenedione, a touch of testosterone, goes into the granulosa cell compartment where FSH is acted on granulosa cells to stimulate the aromatase expression, which converts that androgen into estradiol.

[Slide.]

Now, there are several prismatic examples that I can show you of the essential role of LH in

this process. One way of look at this is to take a look at ovaries that cannot respond to LH, and that has been studied in a mouse model. Indeed, there are humans who share mutations in the LH receptor, who have a similar phenotype, but this is dramatically shown here.

Here we have a mouse who has no LH receptor, so it cannot recognize LH action on the ovary. This is the uterus, it's hypoplastic, and it's hypoplastic because of the absence of estrogen compared to the Wild Type animal.

If we look at the ovaries of this animal, there is some follicular development, but only to the early antral stage, and indeed if we look at higher power, we see these antral follicles, but no corpora lutea, the animals can't ovulate, they can't luteinize. Here, in the Wild Type, we see multiple corpora lutea.

[Slide.]

Now, as I mentioned, this is a phenotype that is also seen in humans, the rare humans with homozygous mutations in the LH receptor.

Clinical experimentation validates, which I have just shown you, in animals and humans. Here we have a severely gonadotropic-deficient patient

who has been treated with recombinant FSH alone, each one of these green bars representing a 75 IU vial.

What you see here is that exogenous FSH accumulates in the patient's blood, and there is follicular expansion, follicular growth, because that is the primary action of FSH, and the ovals here show the follicular size by ultrasound, and you can see that you get a follicle or follicles that reach the pre-ovulatory size.

However, in the absence of LH in these individuals, estradiol levels remain virtually unchanged. Importantly, they are below the threshold level that we know that is essential for stimulating endometrial proliferation. That is about 100 picograms of estradiol per ml.

Indeed, if you look at the endometrial thickness by ultrasound, it doesn't change, and it remains below about 6 millimeters in diameter, and that is a threshold level which one wants to achieve to have a permissive, a receptive uterine environment.

[Slide.]

I am going to take the same type of patient and do the experiment now, not only with

recombinant FSH, but adding back recombinant LH, and what you see here is yes, FSH levels increase, there is follicular growth, follicular expansion, but more importantly, we now have estrogen production, a consequence of adding LH to the stimulation protocol.

More importantly, now we have an appropriate endometrial response, endometrial proliferation that would be consistent with an environment that could support implantation. Indeed, if one wants to achieve pregnancy, one has to consider that, as well, in addition to the growth of the follicle.

[Slide.]

Now, there are some subtleties to the actions of LH, and Dr. Toner referred to this as the "Goldilock's Principle" yesterday. I prefer to think about this in terms of a window, but we are talking about the same thing.

There is a level of LH that supports normal follicular growth, normal androgen production and therefore normal estrogen production, and normal oocyte maturation.

If the LH level is below that threshold, and I think that is clearly characteristic of those

patients who are apulsatile in terms of their LH secretion, 1.2 IU or less LH, there is impaired follicular growth, inadequate estrogen production, therefore, inadequate support for the endometrium, and also there is evidence for impaired oocyte maturation.

There may be a ceiling, and Dr. Toner mentioned this, over which additional LH does you no good and may, in fact, do some harm. That is a result of suppression of granulosa cell proliferation because LH causes granulosa cells to differentiate.

There may be promotion of follicular atresia of non-dominant follicles, and that actually could turn out to be a good thing, but premature luteinization of the pre-ovulatory follicular, an impairment of oocyte development are not good.

So, we want to be in the right zone in terms of the therapeutic window for LH administration.

[Slide.]

What are our current options for the treatment of HH? That was touched upon earlier today. We talked about gonadotropin-releasing

hormone can be used in women with an intact pituitary. Unfortunately, it is not available.

Gonadotropins. Gonadotropins containing both FSH and LH activity, human menopausal gonadotropins have been used to treat these women in mostly very small and uncontrolled studies. The virtue of gonadotropin therapy is that it can be used in women with lesions either in the hypothalamus or the pituitary gland, but as we have heard yesterday, gonadotropin therapies do have some drawbacks.

In the case of hMG, there is a fixed ratio of LH and FSH activity in a single file. What that does is it compromises the capacity of the treating physician to individualize or titrate gonadotropin treatments in these patients, and I know Dr. Santoro is going to touch on this when she speaks to you.

There are some risks of gonadotropin therapy, were mentioned yesterday - ovarian hyperstimulation syndrome, but I would just leave you with the thought, and this is an important one from my perspective, that in treating women with HH, if you get a response even though it's an exuberant response and may cause you to cancel a

cycle, you know that that patient is capable of responding to your therapy, and you can use that information to readjust your protocol in a subsequent cycle.

Multiple gestations, a concern. Hopefully, with improved titration of gonadotropin therapy, that can be avoided.

[Slide.]

Now, what are the unmet medical needs? As you know, in the United States, there is no FDA-approved LH-only treatment for the profoundly LH-deficient patient, and what that does is compromise treatment, I believe, in terms of the individualization, the titration of gonadotropins, which is important to the success of the outcome.

The product before you today is a recombinant product that has some distinct advantages to both the clinician and the patient, first of all, with respect to purity and consistency, one is not dosing patients with material that has been assayed by a bioassay with a significant coefficient of variation.

There is great assurance that each vial contains the same activity, and, of course, these gonadotropin preparations could be administered

subcutaneously, which as we heard yesterday, is a distinct advantage to the patient.

[Slide.]

So, in conclusion, I think there is compelling evidence that LH is required for follicular competency, some threshold level with LH.

We talked about HH as a very rare disorder and it is heterogeneous and it is appropriate to identify the subgroups of patients within the HH broad category who are going to require a specific therapy and, in this case, combined gonadotropin therapy.

The evidence that you will hear today and that I have presented briefly is that the profoundly HH-deficient woman will required exogenous LH for normal follicular function, and again, for the benefit of both the clinician and the patient, the ability to optimize therapy by individualization and titration of gonadotropins is paramount for successful treatment of these individuals.

I will now turn the podium over to Dr. Paul Lammers, who is the Chief Medical Officer of Serono, to discuss the clinical development program

with you.

Luveris Clinical Development Program

DR. LAMMERS: Thank you, Dr. Strauss.

Madam Chairman, members of the committee, I appreciate the opportunity to me today to provide with you an overview of the most pertinent data that we have assembled at Serono over the past 10 years on recombinant LH or Luveris.

[Slide.]

What I would like to do for you is provide you a brief overview of the clinical development program and go over some of the considerations that went into the study design and in the treatment, and also explain how we came to our definition of treatment effect and the study endpoints that we used in our studies.

Then, discuss the results on the dose finding study on the efficacy confirmatory trial 21008 with its extension study 21415.

Finally, provide a real brief, one-slide summary of safety, and then end with some overall conclusions.

[Slide.]

This table is also provided in the briefing package that you have received, summarizes

the six studies that are totally included in this development program.

They are summarized here in two different groups. The top four basically identify those studies that included the profoundly LH-deficient patients that are defined by an LH level of below 1.2.

The two bottom ones, 6905 and 8297, are two studies with a more broader hypo/hypo population, and therefore present a different patient population.

I just want to bring your attention to this column here, Number of Patients. If you look in the literature on hypo/hypo, most case series, or the few that have been published, perhaps include eight or nine patients.

Here, you can see that Serono truly has assembled the largest database so far on women with hypo/hypo.

[Slide.]

Now, when I show you results, we are back in time, but I would like to take you back at the beginning of this program and just briefly mention the challenges that any company has when you embark on a new clinical development program for a new

product, especially in such a rare orphan population as hypo/hypo.

The issues at hand were that what we were faced with had an impact both on our study design and also how these patients were going to be treated as part of the study protocols.

First of all, our intent was to try to identify a clear dose response in our study. Obviously, since these products are given together, so we have LH that has been added to FSH, which means you have two active products, however, we wanted to focus on the effect of LH alone.

That is why we fixed the dose of FSH in these cycles, which is contrary to what clinicians do in practice where they tailor the dose of FSH to the individual patient's response, but we did want to have the potential confounding effect of a change in FSH dose. That is why we fixed the dose.

At the time that we started, there was very limited information on these patient populations, so we didn't quite know how these patients would respond to treatment. We did want to ensure that we had adequate follicular growth and therefore we fixed the dose of FSH at 150 IU/day.

However, because of the fact that we had this fixed dose of FSH, without the possibility of down titrate in case a patient showed an exaggerated response, the investigators supposed the fact that we would put more conservative criteria in place in the protocols to cancel a cycle in case there was an over-response and there was a risk of potentially developing OHSS if treatment would continue.

[Slide.]

The primary endpoint that we used in our study is a composite endpoint that truly captures, as Dr. Strauss showed you, the different actions of LH on the growing follicle. It works with FSH and follicle growth. We use a cutoff for a normal pre-ovulatory size lead follicle of 17 mm or greater. It works to support steroidogenesis and therefore we measure E2.

We used a cutoff of 400 pmol/L in the European study, which we then consistently also used in the U.S. studies, but now it was converted back to picograms/ml, which gives you this somewhat odd number of 109 pg/ml, but it stems from the conversion.

This level represents the lower limit of

normal and it is adequate for endometrial growth, as Dr. Strauss just mentioned.

Finally, the contribution of LH to corpus luteum competence after administration of hCG. We used 25 nmol/L in Study 6253, the European study, which was similarly converted back to U.S. standard of 7.9 ng/ml.

FDA indicated to us they like to see the 10 ng/ml cutoff, however, since none of the patients in any of our studies had a level in between the two, whether we take the 7.9 or the 10 ng/ml doesn't change the outcome of our results and clearly both of those, the 7.9 and the 10 are clearly above the threshold for normal ovulating women of 6 ng/mL.

[Slide.]

The way we defined success in our protocols is really critical and pertinent to the discussion today. I just showed you the three parameters of our composite endpoint of follicular development, however, if the patient did not meet all three criteria, as an example, if hCG was withheld, but she went on, then, pregnancy was always considered an important endpoint.

So, if she didn't meet all three, however,

if the patient became pregnant, that obviously was a success because ultimately, that is the ultimate outcome of these studies.

If the cycle was canceled for risk of potentially developing OHSS, it also was considered a success since, as Dr. Strauss mentioned, an ovarian response in these women, especially women with primary amenorrhea who may never have had any ovarian response, it is a positive sign, and, in fact, provides a measure of titrating the dose in subsequent cycles of treatment, so this is a good sign for clinicians and for the patients because it may set the tone for the next cycle.

Looking here at the cutoff values, Dr. Keefe presented yesterday an E2 in a controlled ovarian hyperstimulation scenario of 3,500 pg/ml. Obviously, for ovulation induction is lower. In clinical practice, people use 2,000 or 2,500 as a cutoff.

We were more conservative and set at 1,100. Again, the reason is that we had a fixed dose of FSH that could not be down-titrated.

[Slide.]

The key secondary efficacy endpoints that were used in the study were estradiol level per se,

endometrial thickness, and pregnancy rate.

[Slide.]

Turning then to the results of our dose finding studies.

[Slide.]

Study 6253 was the first study conducted as part of this development program. It was a controlled, parallel-designed, open-label, randomized, 3-cycle, dose-finding study conducted in Europe and Israel between 1993 and 1995, an enrolled 36 subjects in four countries.

We used a standard dose-finding approach. As I mentioned, we fixed the dose of FSH at 150 IU/day to which we added either no, 25, 75, or 225 IU of Luveris per day, randomized equally across the first cycle.

The protocol pre-specified that Armitage trend test to detect a relationship between the LH dose and follicular development in the first cycle, and was adequately powered at 85 percent.

[Slide.]

The clinical entry criteria used for Study 6253 was the patients needed to have clinic amenorrhea of six months or longer, combined with low gonadotropin levels as indicated by an LH below

1.2, an FSH below 5 IU/L, truly profoundly gonadotropin-deficient patients.

Also, they needed to have a negative progestin challenge test as an indication of chronic low estrogenic status.

Treatment duration was up to 14 days with the proviso if at day 14, there was signs of follicular development, treatment was allowed to continue.

We analyzed our primary and secondary endpoints based on Cycle 1 information, however, pregnancy was evaluated across all three cycles.

[Slide.]

It is important again to realize, going back to Dr. Layman and Dr. Liu's presentations this morning, the sometimes severe pathologies and underlying deficiencies in these patients.

The 38 patients included in 6253, as you can see here, the breakdown into either primary or secondary amenorrhea, there were 28 patients with primary and 10 patients with secondary amenorrhea included in the study, and again the underlying deficiencies clearly showed that these deficiencies truly block these patients' ability to achieve their goal of pregnancy.

[Slide.]

If we look at the results for 6253, at first glance you see a clear dose-response curve. This trend was high statistically significant. If you take a linear trend or any other reasonable trend, the statistical significance is maintained which shows the robustness of this data.

If we look at the individual dose group results, 1 out of 9 patients responded to the FSH alone, which is in line with what is reported in the literature that about 10 percent of patients could respond to FSH treatment alone.

If we look at the 25 IU dose group, 2 out of 8 or 25 percent response, which is as you can see about twice as high as the placebo response, however, it is not clinically nor statistically different from the placebo response.

The steep rise, however, in the dose-response curve occurs at the 75 IU dose where now 7 out of 11 or 63 percent of patients respond to this treatment with the 75. This is four to five times high response than placebo and two to three times higher than observed for the 25 IU dose.

Tripling the dose from 75 to 225 IU of Luveris only adds a marginal incremental benefit in

terms of follicular development. So, it seems almost that we are topping off here in terms of the dose-response curve.

[Slide.]

The design of 6253 allowed us to also look at the individual dose groups, at how patients individually responded if they were treated with different levels of Luveris.

This slide gives an example of this. There were 10 patients who, in Cycle 1, participated in the 225 IU dose group. Out of these 10 patients, 2 patients showed no follicular development, 5 out of 10 had adequate follicular development and went on to receive hCG, 3 patients had an over-response, therefore, their cycles were canceled due to risk of potentially developing OHSS.

These 5 responders, adequate response, were then in Cycle 2 treated with the 25 IU dose, and then only 1 out of these same 5 patients responded. Out of these 4 who didn't respond, 3 went on to participate in Cycle 3, were given the 75 IU dose, and now all 3 patients responded.

So, it clearly shows that in order to have an adequate follicular development, they need to be

at the 75 or 225 IU dose, however, as I showed you in the previous slide, the 225 doesn't add that much more.

Also, it is important to know that in the first cycle, 1 out of 5 patients respond on 25, here again we see the same thing on the 25 IU dose. Only 1 out of 5 patients responded.

[Slide.]

If we look at the secondary efficacy parameters in the study, if we look at the estradiol levels, you can see again a clear dose response where both the 75 and 225 IU dose clearly surpass the important mark of 109 to 100 pg/ml that Dr. Strauss indicated that is required for endometrial growth.

Again, here we see no difference between the 25 and the placebo dose groups.

This is then translated in an adequate endometrial response on the 75 and 225 IU dose groups, with 75 showing numerically the highest response in endometrial thickness. Both of those, however, are above the 6 mm endometrial thickness that Dr. Strauss indicated is required, is ideal for early embryo implantation of pregnancy.

[Slide.]

Moving then to our second study, Study 6905. This was a controlled, parallel-designed, open-label, randomized, 3-cycle, dose-finding study conducted in the U.S. between 1994 and 1997, and included 40 subjects enrolled at 14 centers.

Dose groups, again, we used 150 fixed dose of FSH combined again with 0, 25, 75, and 225 IU dose of Luveris again randomized equally across the first cycle.

[Slide.]

Apart from the fact that the clinical criterion of amenorrhea was similar, there are some major differences with the design compared to Study 6253.

First of all, as Ms. Williamson already indicated, the entry criteria for the LH and FSH were relaxed to try to facilitate patient enrollment, and we ended up with an LH cutoff of below 13 IU/L instead of 1.2, and FSH lower than 11 instead of lower than 5.

Also, there was no requirement for a progestin challenge test, so therefore, there was no real indication whether these patients truly had a chronic low estrogenic status.

Finally, treatment duration was allowed to

be up to 21 days instead of 14 days, with the same proviso if at day 21 there were signs of development, she was allowed to continue the treatment.

[Slide.]

If we look at the results of 6905, it is obvious at first glance there is no dose response across the studies, also, there is no different change between the four different dose groups, and the only conclusion we can take from this study, there is no benefit of adding Luveris to this broader hypo/hypo patient population.

[Slide.]

So, at this point in our development program for Luveris, we had completed two dose-finding studies. Study 6253, in the profoundly LH-deficient patient population, where we have shown a benefit of LH, and Study 6905, broad hypo/hypo population, LH above 1.2, no additional benefit.

The results of these two studies were not contradictory, but truly we have shown what we have included two different patient populations with two different responses.

After meeting with the agency, as was

mentioned already, agency requested for us to conduct a confirmatory Phase III trial in which we decided to include the same cutoff level for LH because we have shown, in 6253, that that is the patient population that truly benefits from Luveris.

The reason that we selected the 75 IU dose therefore was based on our Study 6253, where we had shown that the 25 IU dose was not clinically nor statistically different from the zero IU, and we had shown the 75 percent non-response in this dose group.

The 75 IU dose had shown a clinically and statistically different response from the zero IU in primary endpoint with a more than 5-fold increase in patient response and a primary endpoint of follicular development. Also, we saw very clinically meaningful differences in secondary endpoints in terms of estradiol response and endometrial response.

Finally, the 225 IU dose did not provide additional benefit in efficacy compared to the 75 IU dose. So, basically, we can conclude that the 75 IU dose is the minimum effective dose that provides the maximum therapeutic benefit to these profoundly

LH-deficient patients.

[Slide.]

Study 21008 was then followed by a rollover study 21415. This was designed as a two-phased approach, was already intended from the beginning, so we had a placebo, double-blind, placebo-controlled trial, one cycle, after which patients were allowed to roll over in Study 21415.

[Slide.]

Turning then to the results of our confirmatory study 21008.

[Slide.]

This is a double-blind, randomized, placebo-controlled, multinational study in patients seeking pregnancy. In fact, to date it is the only double-blind, placebo-controlled study in hypo/hypo.

We compared placebo, which is now a true placebo, and 75 IU of Luveris, again combined with 150 IU of FSH. Again, we want to keep the protocol as similar to Study 6253 which would enable us also to look for result across studies.

Patients were randomized in a 1 to 2 fashion and again the fixed dose of LH and FSH.

[Slide.]

The clinical entry criteria were identical as those used for Study 6253 and as I mentioned, it was a single cycle of treatment to focus on the primary endpoint of follicular development with the possibility of rollover in the extension study.

[Slide.]

Again, as shown for Study 6253, in the 39 patients enrolled, there was a breakdown of about 20 patients in primary amenorrhea and 10 patients with--or it's just the other way around--I think it's 20 and 20 with primary and secondary amenorrhea.

[Slide.]

If we looked under results of our primary endpoint of follicular development, you can see we get a very consistent response. We see again a 4 to 5 times higher response between the 75 and the placebo group, which difference is both clinically and also highly statistically significant.

We had 2 out of 13 patients responding on placebo compared to 17 out of 26 on the 75 IU dose group, and the 65 percent is very close to the 63 percent in 6253, and the 15 percent of placebo is very similar to the 11 percent on the zero IU dose in 6253.

[Slide.]

Now, after submission of the NDA, FDA indicated to us they felt it was inappropriate to count cycles that were canceled due to the risk of potentially developing OHSS as successes, and therefore they should have been excluded and counted as failures.

If you do that analysis, you get the following results. We still have a 3- to 4-fold difference in response between the 75 IU dose group and the placebo dose group. This difference maintains a statistical and clinical significant difference.

It is important to realize that you see that because of the cycles canceled, you see a bit of a drop in the 75 IU dose group, whereas, you hardly see a drop--well, it only goes from 2 patients to 1 patient on placebo, but this truly indicates if patients do not have an ovarian response, there is no reason to cancel their cycle, so that is why we see the difference here in the 75 IU dose group, but we don't see the difference in the placebo dose group, however, it is important to realize that the clinical and statistically significant difference is maintained.

Now, you may have observed that in the two briefing packages that you received, there are differences in how the calculations are done in terms of success or failure, and also that translates then to different p-values between our analysis and FDA's analysis.

I just want to use these next two to three slides to highlight the differences.

[Slide.]

On the left side you see Serono analysis, on the right side you see the agency's analysis. The numbers I have just shown you are on the left side what we see, but whether we take the cycles canceled as success or cycles canceled as failure, we maintain a statistical significance.

You see on the agency side, the numbers are slightly different. Here, in Dr. Meaker's statistical section, she shows this p value, which is almost consistent with ours, however, if we look at the cycles canceled, the agency has a p value of 0.06, which is just above the 0.05 cutoff, but still borderline significant, the difference, however, being the fact that the agency did not include a patient who achieved pregnancy and therefore should have been included as a success.

[Slide.]

I just want to bring you back briefly to the protocol definition of treatment success. This is an exact quote out of the protocol for Study 21008 and 21415. Again, we had the three parameters of follicular development. I just want to point your attention to the underlined sentence that says, "Should any patient achieve pregnancy, that patient will be counted as having achieved follicular development."

[Slide.]

The patient in the underlined part of this discussion, it was a patient who had an adequate follicular development in terms of a lead follicle of 20 mm. She easily cleared 7.9 or 10 ng/mL cutoff for P4, however, E2 was just below the 109 pg/mL, therefore, because of this, she was not counted as a success on the primary endpoint of follicular development.

However, she was given hCG because again it is up to the investigator, these E2 levels come in later, so if the investigator feels with a lead follicle like this, that it was appropriate to give her hCG, and a month later she had a positive pregnancy test, which was again repeated two days

later and again it was clearly positive.

Now, the ultimate outcome of the pregnancies doesn't take away from the fact that this patient did achieve a positive pregnancy test, therefore, she did have clear signs of follicular development and ovulation, otherwise, she cannot achieve these levels of hCG and of serum pregnancy test. Therefore, she should be included as a success.

[Slide.]

Turning then to our rollover study 21415.

[Slide.]

If patients participated in 21008 in this one-cycle treatment, and if they did not have a serious adverse event, did not have actual ovarian hyperstimulation, and did not become pregnant, they were eligible to participate in a rollover study.

Here, they were given up to three additional cycles of treatment to truly try to achieve their goal of achieving pregnancy. We used a consistent primary endpoint, important, however, difference here, they were given 75, but now an individualized dose of FSH.

This is really how the drug will be used in clinical practice where the dose of FSH will be

tailored to the patient's individual response.

[Slide.]

Out of 39 patients who participated in Study 21008, 31 elected to participate in the rollover study. These 31 can be broken into two separate groups, 11 had been treated in 21008 with placebo, 20 had already been treated in 21008 with the 75 IU dose.

[Slide.]

If we look at the response in terms of follicular development, this graph shows you if you take cycles canceled due to risk of OHSS as success, you see that in the first cycle, they have a 67.7 percent response, again very consistent with 6253 and 21008.

This goes up, it's a cumulative rate, in the second and third cycles to 83.9 and 87.1 percent follicular development overall. However, as I mentioned, now these patients were allowed, the physicians were allowed to titrate the dose of FSH based on their previous cycle response, and it is truly shown here that whether you take the cycle canceled with risk of OHSS as a success or a failure, there is no difference in outcome in the second and third cycles, the numbers are identical.

[Slide.]

So, allowing individualization of the dose, titrating the dose of FSH downwards allows you to mitigate this risk of potentially canceling a cycle. So, cycle cancellation due to the risk of OHSS is a normal precaution in clinical practice. Ovarian over-response is a treatment effect and provides guidance for the next cycle of treatment.

It is important to note that out of 11 patients whose cycles were canceled either in the first cycle of 21008 or in the first cycle of 21415, 4 out of these patients went on--because patients can still go on in subsequent cycles--and 4 out of these 11 patients did achieve pregnancy.

[Slide.]

I mentioned 11 patients that were treated with placebo in 21008 and now in 21415 were given 75 IU dose of Luveris for the first time. They can be considered what we call the LH-naive patient group.

If you look at their different responses in 21008, only 1 out of these 11 had follicular development, she did not become pregnant in Study 21008, however, if they were then treated with the 75 IU dose of Luveris, 7 out of these same 11 had a

response of 63 percent, and 4 out of these 11 achieved pregnancy.

[Slide.]

I know pregnancy is a big part of the discussions yesterday and today, and I just want to highlight the pregnancy results that we have achieved in this rollover extension study.

Thirty-one patients participated, of which 27 continued to receive hCG. In Cycle 1, 11 of these patients achieved pregnancy and 9 in the second cycle, overall, for 20 patients out of 27 who received hCG, which is a pregnancy rate of 74.1 percent.

[Slide.]

If we are looking at clinical pregnancies per se, the numbers are 11 pregnancies in Cycle 1, 5 in Cycle 2, overall, 16 out of 27 for a 59 percent clinical pregnancy rate, which is an excellent rate in these difficult-to-treat patients.

[Slide.]

Looking overall the pregnancy results in our studies, this slide summarizes the three studies that are really pertinent to this discussion of the profoundly LH-deficient, 6253,

21008, and 21415.

If we look at the results here, you see that out of 22 patients treated with placebo or FSH alone, 2 patients achieve a pregnancy, of which one was a clinical pregnancy. The 75 IU dose out of 48 patients included here, 24 or 50 percent achieved pregnancy, of which 19 or 39.6 percent a clinical pregnancy.

[Slide.]

In terms of pregnancy outcome, this table summarizes the results. Let me just focus on the largest patient group, which is basically the 75 IU dose group. There were 111 patients in total included in our program that were seeking pregnancy treated with the 75 IU dose of Luveris.

Out of those 111, 51 achieved a pregnancy, of which 44 were clinical pregnancies. These 44 resulted in 35 live births that resulted in 22 singletons, 12 twins, and 1 triplet, and 1 stillbirth.

[Slide.]

Concluding then on efficacy.

[Slide.]

Study 6253 provides the rationale for selection of the 75 IU dose of Luveris as the

appropriate dose for hypo/hypo patients with profound LH deficiency as defined with a cutoff of below 1.2.

We have shown there is no benefit of the 25 IU dose, and there is no additional benefit for 225 IU dose over the 75 IU dose of Luveris.

Study 21008 is the only double-blind, placebo-controlled study conducted in this patient population, which confirmed the efficacy of the 75 IU does in this profoundly LH-deficient patient population.

[Slide.]

The rollover study 21415 supports the efficacy of the 75 IU dose as used in standard clinical practice with individualization of the dosing.

We saw a cumulative follicular development rate of 87 percent and a cumulative pregnancy rate of 74 percent.

Overall, we had a 50 percent pregnancy rate in profoundly LH-deficient women treated with the 75 IU dose of Luveris.

As I mentioned at the beginning, I would only have one slide on safety as the Medical Review Officer at the agency indicated in their briefing

documents the FDA has no concern regarding the safety of Luveris, so I just want to summarize this in one slide. However, we have also provided in our briefing package quite a bit of information on safety and I will be more than happy in the Q and A session should you desire to answer any questions about safety.

[Slide.]

Basically, as I said in the beginning, Serono has assembled the largest safety database in female hypo/hypo patients, 170 patients in total, of which 152 received Luveris in a total of 283 cycles.

There was no increase in adverse events when Luveris is co-administered with recombinant FSH, compared to recombinant FSH alone.

We have seen similar rates of actual OHSS across all dose groups including recombinant FSH alone.

Overall, the safety profile of Luveris is comparable to currently marketed gonadotropins.

[Slide.]

Concluding then overall on our Luveris clinical development program, among women with hypo/hypo, a cutoff value of 1.2 IU/L

differentiates between LH dependence and LH independence.

Follicular development is an appropriate endpoint in this population and correlates with pregnancy as is clearly shown in Study 21415, 87 percent follicular development rate, a 74 percent pregnancy rate.

Canceling a cycle is prudent clinical practice in an over-responding patient with follicular development.

Women with profound LH deficiency clearly benefit from the 75 IU dose of Luveris.

The safety profile of Luveris is similar to other gonadotropins and is not different from treatment with FSH alone.

With that, I would like to invite Dr. Santoro to provide an overview of clinical perspective and risk/benefit assessment.

Clinical Perspective and Risk/Benefit Assessment

DR. SANTORO: Good morning, Dr. Guidice, and good morning to the panel.

What I would like to do is provide some of the clinical perspective on the use of recombinant LH as someone who has been treating patients with hypo/hypo and probably has a case series of about

30 such patients over 20 years in practice.

[Slide.]

Hypogonadotropic hypogonadism, the typical clinical patient that comes into the office when it is a severe disorder has primary amenorrhea, she is in her teens, she comes in accompanied with her mother, and she has a complete absence of pubertal development and amenorrhea.

Both mother and daughter are very worried because they feel that something is severely wrong that needs to be addressed and that perhaps multiple treatments are needed. It is sort of a white knuckle affair in the office.

When I get to tell them on the basis of my history and physical and biochemical testing that it's a single endocrine factor and that in most cases they are solely deficient in gonadotropin-releasing hormone, there is quite a bit of relief.

Then, when I tell them their potential to be highly fertile when ovarian responsiveness is restored, usually, since my patient is teenager, she is not that worried about that, but her mother starts to weep with relief that this is the case.

As you saw from Dr. Lammers' data, the

very high fertility rate in these patients seems to be a general finding clinically. We do know that both gonadotropins, as Dr. Strauss has pointed out, LH in addition to FSH are needed to optimally grow follicles in these women, and the induction of follicular development is a prelude to fertility, and is the therapeutic goal, as a clinician, I cannot guarantee pregnancy to my patients, but I can induce follicular development, you must have follicular development, it's an obligatory step on the way to pregnancy.

[Slide.]

In follicular maturation, FSH induces early growth of follicles as we have seen, and controls the follicle number, and that is an important point that has not been emphasized, and I will emphasize that in the next slide.

LH provides the estrogen precursors and therefore allows for estradiol to be secreted, and is needed for the latter stages of follicle growth.

[Slide.]

When one gives recombinant FSH only to women with profound LH deficiency in hypo/hypo, one sees follicle growth, but no estradiol, so with escalating doses of FSH, serum FSH goes up, nothing

happens to estradiol, as Dr. Strauss showed, but look at what happens to follicles.

This is a cohort of growing ovarian follicles, and the follicular size and number is large, and that is influenced by FSH. In my training, we used to say that FSH loads the gun, because it makes all these follicles.

This is important in the evolution of these studies because a prospective criterion was to cancel cycles at risk for ovarian hyperstimulation syndrome because we had to fix the dose of FSH and we knew in advance that some women might get too much.

What you see here is the ovary of a woman who has been stimulated, she has three follicles in her single ovary. If she has got three in the other ovary, she has already met my criteria to cancel her cycle because she would then have a total of six and would be at an excessive risk of ovarian hyperstimulation syndrome, which you can see a picture of on the right.

This is a smaller ultrasound picture than the one here. These ovaries are probably 10 to 15 centimeters in size. There is probably quite a bit of acidic fluid in this patient, she is hurting,

and she is sick. She may be hospitalized and is at risk for even more dreadful problems like a pulmonary embolus.

As a clinician involved in a study like this, I would not want to give a patient like this hCG because I might create this sort of a problem. If I gave hCG, could I obtain a progesterone level of 10? I am pretty confident that I would.

Might this patient get pregnant? She might, at a very high pregnancy rate, but she might wind up with this, and therefore, ethically, we needed to make conservative criteria to withhold hCG under such circumstances.

[Slide.]

In HH patients, we have to have no gonadotropins, so you have to give back what is missing. Since most of these women are solely deficient in gonadotropin-releasing hormone, that has been shown in the past to be highly effective when the pituitary gland is intact, but, alas, is not available in the United States.

Alternatively, exogenous gonadotropins can be given in the form of hMG, but there is a fixed ratio in the combination medication. Almost all except for one of these has to be given as an IM

drug, and that is a limitation to treatment.

My patients overwhelmingly prefer sub-Q medications that they can give themselves, and our current strategies do not allow for the circumstance in which I can fix the dose of LH at 75 IUs, but I might have to give less than 75 IUs of FSH. There is currently not a way to do that unless both medications were split.

So, the optimal strategy for patients clearly is to have stand-alone recombinants that allow the titration and individualization of medication that happens in real life reproductive endocrine practice.

[Slide.]

LH is permissive and is obligatory for follicle growth in profoundly LH-deficient women. I know clinically that I must tailor the FSH dose that I give to my patients in a gonadotropin cycle. In fact, my brain is the sole source of feedback to my patients' ovaries when I get the estradiol results every day, and once a day is a little too slow sometimes.

I may have to go down and I may have to go up. So, I need to be sure that I am only changing one thing at a time. It would make it impractical

to be fiddling with both FSH and LH.

So, in fact, in practice, we do the opposite of what was done in the clinical trials. We move the FSH, and I would like to keep that LH fixed at an effective dose, so I don't have to worry about it, and I think Dr. Lammers has shown you enough evidence that the 75 IU dose is an adequate one.

This strategy then maximizes the return on the investment that a patient and clinician makes in a cycle, which is expensive, which involves a great deal of effort, and which sometimes involves a learning curve.

[Slide.]

The risks and benefits have been briefly touched upon, but the risks of LH are those that are the known complications of gonadotropins in infertility treatment, and these include ovarian hyperstimulation syndrome, which is to be avoided and can in many, but not all, cases be avoided by withholding hCG, and the risks of multiple births.

There were other minimal or transient treatment-related adverse effects that were generally minor, and the general risks of gonadotropins can be mitigated with proper

diagnosis and attention to dosing and very careful observation of the patient.

[Slide.]

The benefits of a stand-alone LH is that optimal folliculogenesis and an optimal endocrine profile can be based on individualized treatment.

The convenience of a sub-Q preparation, particularly if it can be mixed with the FSH, is that patients can give themselves a single daily shot of meds that they can control themselves.

The safety profile of LH is comparable to other gonadotropins that are currently on the market, and they are associated with a high pregnancy rate particularly in this patient population.

[Slide.]

So, to summarize, this is a rare patient group, but in this patient group, it is critical to give them LH during the process of folliculogenesis.

The provision of recombinant LH to recombinant FSH allows the maximum flexibility in the treatment of these patients, which is what we, as clinicians, need, and will be much more convenient for patients.

The benefit-to-risk profile is therefore in favor of approving this product and making it available to women who have hypo/hypo.

Thank you. I would like to turn over to Ms. Williamson to conclude.

Summary and Conclusions

MS. WILLIAMSON JOYCE: Thank you, Dr. Santoro.

[Slide.]

As we close our presentation today, I would just like to touch on a few of the points that we have shared with you and hoping that we have been able to provide some clarifications and have provided some additional information.

First and foremost, I believe that the presentations that were made both yesterday and then again by Drs. Strauss and Santoro have clearly indicated that there is a need for LH in treatment of patients with the rare condition of HH, and in particular, those patients that are considered to be profoundly LH deficient.

We also believe that based on these data, that the appropriate patient population has been identified. Through our clinical trial results as shared by Dr. Lammers, we believe that we have

identified and studied, and have proposed the optimal dose of treatment for these women, which is 75 IU/day, and that that dose is both safe and effective.

Importantly, we continue to believe that follicular development is an important endpoint in treatment of these patients. This endpoint was prospectively defined in our double-blind, placebo-controlled clinical trial and is consistent with the endpoints as studied in our earlier trials.

We believe that follicular development is the appropriate endpoint and provides more information than any other single endpoint because it allows you to determine the appropriate action of the drug under study, which in this case is LH.

Serono, as Dr. Lammers has indicated, has compiled now the most extensive database in studying a recombinant luteinizing hormone in hypo/hypo women. These studies have now totaled 170 women overall during the last 10 years.

[Slide.]

As also mentioned, we have also conducted the largest double-blind, placebo-controlled trial in these patients with this rare condition as

prospectively defined in the protocol that we submitted to the agency.

We believe that this pivotal trial is positive irrespective of whether cycle cancellation due to the risk of OHSS is analyzed as an efficacy success or as an efficacy failure.

Since the original action, we have also provided additional supportive data in our follow-on Study No. 21415, which provided those initial patients an additional opportunity to achieve pregnancy in three subsequent cycles. We believe that this study has also provided important additional supportive evidence in terms of safety, efficacy, and pregnancy.

[Slide.]

Finally, there is no increase in adverse events compared to placebo when administering LH versus FSH alone, and the safety profile is similar to that of other gonadotropin drug products which are currently approved and on the U.S. market today.

We believe and we hope that we have provided sufficient evidence to demonstrate that Luveris is effective in the treatment of these infertile women with a profound LH deficiency, and

provides for a very positive benefit-to-risk profile in support of approving this product.

I would like to thank you very much for your attention today. Our presentation went over just for a few minutes, and we would be happy to answer any questions that you may have.

DR. GIUDICE: Thank you very much. I would like to thank all of the presenters for their very clear presentations. I will now open up the discussion for questions from the committee, please.

Dr. Hager.

Questions from the Committee

DR. HAGER: For Dr. Lammers. You stated that you have shown emphatically, in your own words, that the 75 IU dose was the effective dose. Might I just ask how do you not know that 50 IUs is an effective dose?

MS. WILLIAMSON JOYCE: Dr. Lammers.

DR. LAMMERS: The selection of 75 IU dose as the dose that provides the maximum therapeutic benefit was based on 6253 and then confirmed by Study 21008. Although it is true that we have not studied the 50 IU dose, Dr. Hager, I think that in our dose-finding Study 6253, we have clearly shown

that the difference in response between the 25 IU dose and the 75 IU dose truly supports the 75 IU as the maximum responding dose, also because it really is that part of the curve where you see the maximum therapeutic benefit and increase.

Also, I think it is important to realize there is no safety concern with Luveris, so therefore, I think it is important to provide the patient right away with the maximum or the optimum dose of Luveris, which we clearly think have shown this at 75 IU dose.

DR. SANTORO: I just want to point out that dose reductions, the difference between 25 and 75 IUs is 50 IUs, which is a fraction of an ampule, and those are dose increments that are rarely employed.

So, whether the needle needs to be moved in either direction, I would strongly argue in favor of keeping it simple and leaving it at 1 amp because we know that worked well, because when one is clinically given the medication, I know I have to move my FSH, I want to keep my LH fixed.

DR. GIUDICE: Dr. Rice and then Dr. Keefe.

DR. RICE: You didn't spend a lot of time on looking at the patients in 6905, these patients,

that subpopulation who had the LH less than 1.2, and believe me, it's difficult to look at the data that you all submitted versus what the FDA submitted, and make sure we are looking at the same tables, so I am trying to make sure of that.

But when I look at the data, if I pull those patients out of 6905, who had an LH of less than 1.2, of those five patients, 100 percent of them actually have follicular development. It took them on average 20 days to get to that follicular development with 25 versus an average of 10 days of the patients who were given 75, but they still got there.

Now, my concern is that the incidence of OHSS, though, in those patients receiving 75 IUs was 21.7 percent, and I assume that is using your definition of three follicles greater than 15 and/or that estradiol level, but when the patients with 25 IUs was, it was only 11.8 percent. That seems like a significant jump in my opinion for an additional 10 days of treatment.

So, I guess I am not convinced that there is not room in there where you could have 25 IU of LH as the dose, and then you increase that appropriately, because you clearly show that even

when you maintained 150 IU of FSH, that you got adequate follicular development at 75 IU and some at the 25 IU, so you could titrate up the LH and perhaps be, quote, unquote, "safer," as you define OHSS.

MS. WILLIAMSON JOYCE: I think I would like to have Dr. Michael Diamond comment on that, but, first, I would just like to clarify. In terms of OHSS, are you referring specifically to the risk of OHSS or actual OHSS?

DR. RICE: From what I see from the data here, it says 21.7 percent, 20 of 92 patients across all the population receiving 75 IU experienced OHSS as defined in the clinical.

MS. WILLIAMSON JOYCE: Thank you. We will clarify those numbers.

Dr. Diamond.

DR. DIAMOND: I think it's important not to confuse the issue of risk of ovarian hyperstimulation syndrome with just an exaggerated response with actual occurrence of ovarian hyperstimulation syndrome. In fact, the incidence of ovarian hyperstimulation syndrome in the patients who were treated with Luveris was actually no different than what is available for other

gonadotropin formulations which have been approved.

So, that is I think part of response to your question. The other issue is about the patients within 6905 who had the low LH levels. As you have correctly identified, there are a subgroup of those patients who did respond, but required much longer duration of therapy.

Normally, when we give gonadotropins, as you know, normal duration of therapy is going to be 9 days, 10 days, 12 days. Twenty days is much longer than we would conventionally give for patients. It requires them to come to the office many times for monitoring first thing in the morning, disrupting their normal activities, taking them away from their work, and so there are lots of patient inconveniences for that.

The other component of that to keep in mind is that among those patients, if you had limited it to 14 days of therapy, which is what was done in the pivotal trial and which is a more conventional length of therapy, among those patients who received 25 IUs of LH in combination with the FSH, only 4 out of 5 of them would have gotten actually to a point where they had follicular development.

MS. WILLIAMSON JOYCE: We do have that data for you, and I do want to clarify that the numbers to which you were referring are not the actual OHSS patients. They are the ones that were at risk.

DR. RICE: I am looking at your information now on page 49, and you have three patients who had OHSS at 75, and zero patients who experienced OHSS at 25. So, there is still a difference, zero compared to 4.7 percent, or if you look at it as the FDA looked at it, I guess they looked at it by risk, 20-some percent versus 11 percent.

So, the question that comes to mind to me, are we comfortable with the fact that we may eliminate our significantly decreased OHSS by using a lower dose for a longer period of time versus having a risk of OHSS by starting with that higher dose.

DR. LAMMERS: Again, I just want to go back to the fact what Ms. Williamson just pointed out. I think we clearly need to differentiate between actual occurrence of OHSS, which I can show you in a minute is not different between the dose groups, that is one thing, but compared to cycle

cancellation, again, we had to imply very conservative criteria because of the fixed dose of FSH in these studies.

So, therefore, I think we clearly need to differentiate between the cycle that was canceled for the risk of potentially developing OHSS, it didn't mean, as Dr. Santoro said, that she would go on and develop OHSS compared to the actual cases.

[Slide.]

This slide summarizes the actual cases of OHSS across our studies. As you can see here, the number of patients in the top row, out of 118 patients, 75, if you look at the percentage patients, because, of course, we had the highest number of patients and cycles in the 75, if you on a percent patient basis or percent of cycles, you can see here there is no dose-related increase in their response of actual OHSS. This number of 5.9 percent is very much in line what is known for other marketed gonadotropins.

So, in terms of OHSS risk, that risk is no different.

DR. RICE: These are people who actually had it.

DR. LAMMERS: Right.

DR. RICE: So, that's not risk.

DR. LAMMERS: These are actual. You see in our overall 10-year program, there were 11 cases of OHSS, of which there were 7 on the 75 dose, but given the number of patients and cycles, this translates in an incidence rate, either percentage or cycle, this is very comparable to the other dose groups.

DR. RICE: But I want to make clear that what you are showing me is incidence of actual occurrence.

DR. LAMMERS: Right.

DR. RICE: And what they are reporting is actual risk, I assume, and I am sure they will clarify that with their presentation.

DR. GIUDICE: I would like to also point out that with zero LH and 150 IUs of FSH, there was a case of severe OHSS, so in thinking of whether it is the actual occurrence or the risk of the occurrence, as I read the data, we are really looking more towards the fixed FSH as problematic for the risks for OHSS.

Are there other questions from the committee? Dr. Keefe and then Dr. Emerson.

DR. KEEFE: Just to put this OHSS story in

context, I have a question for Dr. Santoro.

It seems to me the absence of significant amounts of endogenous LH, when you see it coming down the pike, it is pretty easy to manage, right, you just don't trigger, they don't get pregnant and it sort of probably melts away? It is probably easier to manage these impending OHSS situations than it would be in normal circumstances with these patients.

Was that your experience? As long as you saw the gun overloaded, you didn't pull the trigger?

DR. SANTORO: Exactly. My clinical training was FSH loads the gun, hCG pulls the trigger. So, if you have got the loaded gun, you can still avoid pulling the trigger, but once you have given that, you can't take it back.

DR. GIUDICE: Dr. Emerson.

DR. EMERSON: Two questions. One, I don't know the doses of any of these preparations, but is it possible using hMG to titrate this, such that hMG, in combination with FSH, would get the appropriate ratio of LH and FSH?

If you gave hMG at the appropriate dose for LH, that would be too much FSH?

MS. WILLIAMSON JOYCE: Dr. Santoro.

DR. SANTORO: It can be in the following circumstance. HH women, in general, are very sensitive to gonadotropins to FSH. They are often petite, and you can overdose them with 1 ampule.

So, if I have someone who needs less than 75 IUs, and I can't give her less than 75 IUs of LH with any currently available preparation--I mean I can't give her the 75 IUs, I am sorry. So, if I need to give her the 75 IUs of LH on the basis of these studies, but she needs a half or 37.5 of FSH, there isn't a way for me to do that now.

DR. EMERSON: And then the other thing that I would like to return to is you presented some data about pregnancy rates in the extension trial, and they were not really broken down the way that would be most appropriate, which would be by randomization, that we could evaluate that entirely by randomization since the people went there, that we could still look at those effects and, you know, just some things I was trying to pick up was what was the cumulative pregnancy rate by randomization group for the extension trial or for both trials combined.

Then, I couldn't also figure out was this

pregnancy rate chemical, clinical, live birth, could it be broken down by that.

MS. WILLIAMSON JOYCE: So, as I understand your question, you would be interested in understanding the breakdown of the pregnancy rate in the extension study based on randomization, and you would also like to know specifically whether the pregnancies were early pregnancies, clinical, and what the outcome was.

DR. EMERSON: And actually not just the extension study, I would like it combined with the original study, as well, per cycle.

MS. WILLIAMSON JOYCE: Fine. I would like to invite Dr. Susan Kenley, who is our worldwide director of biostatistics to answer your question.

DR. KENLEY: Good morning. There was no randomization in the extension study.

DR. EMERSON: Excuse me, there was randomization in the first study, and that randomization still holds.

DR. KENLEY: Okay. So, you are interested in the pregnancy rate for the 11 patients that were randomized to placebo in the first study and how many of them got pregnant in 21415 compared to those randomized to 75.

DR. EMERSON: That's correct.

DR. KENLEY: Do we have those numbers? Just to mention--

DR. EMERSON: I guess another question that I would like to ask is also has the FDA reviewed that data.

DR. KENLEY: No, we have not provided a summary of that data. I don't know if they have done that on their own.

DR. GIUDICE: On page 54 of the gray briefing document from Serono, there is a table. Dr. Emerson, does this answer over here?

DR. EMERSON: I don't know.

DR. SHAMES: As a point of information, the original application did not have this.

DR. KENLEY: Can I make one comment while we are working on that? Dr. Lammers showed that in 21415, 4 out of the 11 patient randomized to placebo got pregnant in 21415. Since there were 31 patients in that study, that means that 20 randomized to 75 went on the 21415, so that means that 16 of those obtained pregnancy, and that is a total pregnancy rate.

DR. EMERSON: And that is chemical pregnancy, clinical pregnancy, live birth?

DR. KENLEY: A total pregnancy rate whether it be early pregnancy or later pregnancy.

DR. EMERSON: So, that's chemical.

DR. GIUDICE: It sounds like it's at least chemical

DR. EMERSON: You don't have live births without chemical pregnancy, isn't that true? Okay. I just wanted to make certain that these were hierarchical.

DR. LAMMERS: Dr. Emerson, perhaps I can summarize this.

[Slide.]

This table summarizes for Study 21415, the cumulative total and clinical pregnancy rate that is mostly determined by a positive ultrasound of fetal sac with or without heartbeat. You can see here, in Cycle 1, there were 11 out of 31 cumulative became pregnant, and they were cumulative basis, and out of these total pregnancies, the clinical pregnancy, all 11 were clinical pregnancies.

In the second cycle, 20 out of 31 totals, 16 out of 31 clinical, so there were basically 4 biochemicals in here in the second cycle.

In the third cycle, again, we stated that

there were no additional pregnancies in the third cycle, so basically, you can see here, the majority of these pregnancies were clinical pregnancies.

DR. EMERSON: So, there were 4 who were initially randomized to placebo--

DR. LAMMERS: Correct.

DR. EMERSON: --who in the second or third cycle, I guess first, second, or third, were any of those the same? I believe there was one pregnancy in the placebo group in the first cycle?

DR. LAMMERS: That is correct.

DR. EMERSON: Were any of those the same patients?

DR. LAMMERS: No.

DR. EMERSON: So, there were a total of 5 in the placebo group.

DR. LAMMERS: Correct.

DR. EMERSON: And then the remainder must be then 16.

DR. LAMMERS: Correct.

DR. EMERSON: And what about the one person in the other group?

DR. LAMMERS: We only had the placebo group and the 75 IU dose group.

DR. EMERSON: But in the first cycle under

the randomized trial, there was one patient in each group who--

DR. LAMMERS: No, there were two pregnancies in the 75 IU dose group. One was an early, one was a clinical, and there was one pregnancy in the placebo group.

DR. EMERSON: So, are those two in addition to the 16 that are in 21415?

DR. LAMMERS: Yes, they are.

DR. EMERSON: The point I am trying to make here, for the committee, this is exactly the point I was trying to say yesterday, about how to analyze these data. Once you have randomized, that randomization holds, and so long as you are treating all the rest of the patients the same after that point.

I don't when the blinding stopped and if the placebo patients were unblinded in that second trial, but I am going to act as if they had done this in the fashion.

DR. LAMMERS: Right.

DR. EMERSON: It would be perfectly legit to design the study in which you did randomized, placebo versus drug, and then after that, took everybody and put them on active, and if you saw a

difference at that point, the only thing that explains it is that absence of therapy in that first cycle.

So, if we are seeing differences between the placebo group and the treatment group as randomized, as the trial progresses, and if we can trust this, you know, lack of blinding and other elements like that, that is where there might be any evidence here.

This lack of randomized trial in this extension treatment, if I could have three wishes, one of them certainly would be to convince people that they are hurting themselves in these extension trials if they don't continue to gather information about the randomization that went forward and that the best way to present this data would be to look at that.

We are looking at--and you already know that I am in favor of live births as an endpoint instead of these earlier ones--but there is some evidence of this. It hasn't been reviewed by the FDA, I am gathering, so, you know, it's not there, but this is an important point here, and the non-randomized issues are--

DR. LAMMERS: Dr. Emerson, I just want to

point out that, of course, we look at the data overall, and I think it is important to note whether you look, we see there were far more clinical pregnancies than early pregnancies or biochemical pregnancies.

But overall, I think that out of the 111 patients on the 75 IU dose, there were more than 50 pregnancies, of which 44 became live birth pregnancies, so that live birth rate is an excellent rate in these profoundly LH-deficient patients.

DR. EMERSON: Live birth rate is which?

DR. LAMMERS: Out of 44 clinical pregnancies that were established, 35 became live births.

DR. EMERSON: I am just bringing this up as this is an issue that needs to be addressed. I don't think that the presentation of the data here is, you know, my back of the envelope analysis, I don't think is adequate. I am just saying that there are these points that need to be addressed.

The other issue that I would like to address, though, is--I said if I had three wishes, that that would be one--the second would be that nobody use the word "clearly" for any of these

data, and that will hold on both sides.

This finding the dose, some data was presented that showed in the one study where you started out with 10 patients at the 75 dose, and then you basically challenged them at 25. I would have to look at this. I am sorry, this was of your Cycle 225, where you took the five patients who had what you called "adequate follicular development," and then dropped them down to 25, and then raised them up to 75. This is Slide 44 in your presentation.

Many statements were made about this conclusively shows something. Let me put this data in its proper framework. Let's just imagine this was randomized data, so it's not randomized data, there was a lot of selection going on here, but we basically had three samples, 5 out of 10, 1 out of 5, and 3 out of 3, and all of those are compatible with the exact same success rate.

This data is just completely inadequate to make the statements about whether the cycle had changed. Do we have any other data that you are using to support these statements that reducing the 75 was bad?

MS. WILLIAMSON JOYCE: We didn't

prospectively design the study to demonstrate that.

DR. EMERSON: Thank you.

DR. LAMMERS: I just want to add, Dr. Emerson, that obviously, our primary analysis falls in Cycle 1, which I have shown basically in Cycle 43, however, if you present this data, clinicians always ask, by the way, what happens if you take the patients who didn't respond to this, and look at the other, if you put them through the other data, so this was an example to show if the patients who respond at 225, if you bring them to a low dose, only 4 out of these 5 patients did not respond.

DR. GIUDICE: Dr. Toner.

DR. TONER: I had really just one question regarding the criteria for cancellation. The third element allows cancellation for this risk of OHSS category, but patients with or without LH treatment could end up in that category by virtue of follicle numbers.

You also had an estradiol criterion and I would hope that at least in those treated with LH, that you also saw estradiol production, because follicle growth per se in any of these groups tells you nothing about LH effect, in my opinion. It

presents really the FSH component.

I guess I would like confirmation back that, by and large, those who got the LH had high estrogens, and those who didn't often had low estrogens. I mean you still may have one or two in that non-treated group, non-supplemented group who had it because their own endogenous happened to be high enough.

But I would like sort of a dichotomization of estradiol levels in those two groups.

MS. WILLIAMSON JOYCE: Dr. Lammers.

DR. LAMMERS: Dr. Toner, out of the seven cycles that were canceled due to risk of potential OHSS, there were four patients who had an E2 above the cutoff. The other three patients were excluded because of the number of follicles.

DR. TONER: What groups were they in?

DR. LAMMERS: That was in the Study 21008. That was in the 75 IU dose. There were seven cycles canceled in the 75 IU dose, and that is the ones I am referring to, so 4 for E2, 3 for follicles.

DR. TONER: I understand that, but I wanted to know how that intersected with whether they received LH or not. So, you may have to look

back through your papers.

DR. LAMMERS: There was one patient in the placebo whose cycle was canceled, and that was due to the follicle numbers.

DR. TONER: I guess I would have an objection to including them as successes if they got LH, but were canceled only because of a number of follicles. If they had five follicles, but had no estrogen production, and you were calling that a success, I would argue with that.

DR. LAMMERS: Okay. Dr. Santoro, would you like to comment on that?

Could you rephrase your question, Dr. Toner, for Dr. Santoro?

DR. TONER: Sure. The thing that drives the cancellation risk for this study can be number of follicle only, so you can see that in both the LH treated and the LH not treated group.

If we are really asking the question of whether the LH is working like we hope it would work, we would expect always to see adequate estradiol production in those high-response cycles who were treated with LH. I would just like to know that those cycles that got canceled on LH treatment also had good estrogen production.

DR. SANTORO: What I can show you, if you can put the previous one on with the graph from 6253, I mean I was a 6905 investigator, and I was very conservative about canceling people for risk because I think that is what you have to do in a clinical trial like this, so we wanted to be conservative. So, I would probably have canceled them regardless of their E2, but there is evidence.

Can I have the slide on.

[Slide.]

This slide that Dr. Lammers showed before just shows you there is a big difference in the E2 levels in the women, and this includes women who were canceled for OHSS risk. So, this slide includes all of those, and the median, not exactly pre-ovulatory because some of them never got hCG, but there is a big difference, it's over 10-fold.

So, it is what you would expect physiologically. At time these studies were being done, we were sort of learning this, so it was all happening at the same time. Prospectively, we were not sure. We expected that the cycles without LH would do exactly what you said, they would make follicles, but no E2, but weren't positive that was going to happen.

So, just let me put it back in a time capsule into perspective.

DR. TONER: Right. I don't know if there is understanding of my question and I am having maybe a hard time phrasing it correctly.

I would consider success for this LH product to have been met if a cycle was canceled because of large follicle numbers, but only if they were also making estrogen. If they were growing follicles and not making estrogen, then, I would not want to consider that particular effort a success.

MS. WILLIAMSON JOYCE: Given the fact that our endpoint was a composite endpoint, and we did not break down those prospectively, what we can do is show--Dr. Kenley can actually share some information with you.

DR. KENLEY: I think I am understanding your question. You are saying that you consider some of these ladies that were canceled because of risk of OHSS to potentially be successes, others to be failures, and the ones that would be successes would have the high estrogen.

We have not analyzed them as such, but we did do a sensitivity analysis, and I think it will

help to show you that the significance is still there when you consider those patients who were canceled due to risk of OHSS as a 50 percent chance of responding or 40 percent chance, et cetera. We could get the actual analysis for you later on today.

Let me just point out that in the distribution of the data, the one patient on placebo was canceled because of large follicles. The 6 people on 75, 2 of them were canceled because of large follicles, 4 due to high estrogen levels, so let's bring this one up.

[Slide.]

In that summary, you had 2 of the patients on 75 canceled because of follicles, 4 canceled because of estrogen, and 1 on placebo canceled because of follicles.

Now, when you look at this, this is where we looked at the risk of OHSS as a nebulous type area, not all successes, not all failures, and in this analysis, what you see in the middle is when the 1, when it says, "weight of risk of OHSS," and it's given a weight of 1, that means that they are all successes. The 1 means they are all successes, and that is where our p value came at 0.006.

The zero means they are all failures, and that is where the p value is 0.034 although, say, you give them the 50 percent chance of being a success, the p value drops to 0.0064, 25 percent chance of being a success. It goes down to 0.01, and then a 10 percent chance of actually being a success, we go down to 0.011.

So, given the distribution, I think you can see the study would still remain significant if you included half or less of these patients as successes.

DR. GIUDICE: Dr. Stanford.

DR. STANFORD: It is always easier to look at study designs in retrospect than prospectively, and recognizing that, I am not convinced that fixing the dose of FSH was the best way to do the pivotal study.

Given Dr. Strauss' physiologic rationale that he mentioned that LH is critical regardless of the level of FSH, and given Dr. Santoro's clinical rationale that the way this is actually going to be used in clinical practice is by fixing the dose of LH and then varying your dose of FSH, couldn't you design a protocol where you have a blinded dose, fixed dose of LH or placebo, and then you allow the

clinicians to titrate the FSH, you should be able to demonstrate your response, and that would mirror actually how it is going to be used in practice and be more convincing.

So, I guess my question is in a way maybe not fair retrospectively, but if you were to do the pivotal study again, wouldn't you design it that way rather than with the fixed dose of FSH?

MS. WILLIAMSON JOYCE: I would like to have one of our clinicians comment on that, but I think it is important to note that in addition to the design considerations, the number of patients available to be studied in this clinical trial are indeed rare, so I suspect that a clinical trial designed in that manner would require a significantly larger number of patients in that study.

Dr. Strauss, would you care to comment on that, please?

DR. STRAUSS: The issue here is establishing the efficacy of the active agent, and the decision to fix the dose of FSH provided a clear opportunity to establish whether the LH dose indeed was biologically effective and clinically effective.

The sponsor did do the rollover study which did provide information regarding how these drugs would be used in clinical practice, as Dr. Santoro pointed out, so, in essence, the combination of 21008 and 21415 provides the data that you want, again with the limitations of the small sample size that would be available for evaluation.

DR. STANFORD: I guess I would echo Dr. Emerson's comment that if the rollover had maintained the randomization, that would be a more convincing extension, but I guess what I am saying is that that kind of design could have avoided this conundrum of risk of OHSS cancellation and do you call it a success or a failure, or at least minimize it.

I don't know if Dr. Emerson has any comments on whether it would actually require a larger sample size with a varying FSH. It doesn't seem to me that it would, but I am not a statistician.

DR. EMERSON: I don't see that a different treatment suddenly changes what the sample size requirements are to determine an effect, I would do the same calculations no matter which. So, if you

are saying that what was going to be done and what would be more efficacious, would be titrating that dose, then, that is what you should be testing.

MS. WILLIAMSON JOYCE: I would suggest that given the fact that that would provide for an additional confounding factor, it could lead to a different series--

DR. EMERSON: Again, confounding is protected for by randomization. It is not a confounding issue, it's a precision issue, that you might get more precision by having a very, very controlled population if you could manage to do that, but if you can't do that, then, you have the randomization that is protecting you for everything that happens afterwards.

DR. KENLEY: I just want to make sure that this is clarified. Your optimal design would be to have patients randomized to placebo in 75 IU, and stay on those two doses for multiple cycles, stay on placebo or stay on 75?

DR. EMERSON: It need not be, to tell you the truth, but that is where you would have the most power. You are going to get some attenuation of your effect if you allow the crossover, but when you do allow the crossover, that doesn't change the

fact that you are now testing the difference between, if you will, delayed administration of the drug versus taking it right from the very first cycle.

Again, any difference, and this is dependent upon trusting that there wasn't selection on who went forward and things like that. Again, without the FDA having reviewed the data in this way, I am not saying that I can make a judgment on that, but if we pretended that all of this went forward, you can design a trial that is delayed administration of a treatment, and that is what you are testing.

DR. KENLEY: It is already difficult to recruit for these trials, and I think to recruit for a trial where the patient was going to take placebo for multiple cycles would make it much more difficult.

DR. GIUDICE: Dr. Santoro. As the hour is coming to a close for discussion, we will take a few more questions, and then we will modify the program this afternoon, so that the sponsor will have some additional time for additional questions from the committee.

Your comments?

DR. SANTORO: There is a saying that the retrospector scope always sees 20/20, and while the trial was being constructed, which was a while ago, the options seemed to be much more limited in what could be done with these patients.

So, patients are improperly named there, inpatient when they have HH and they want to get pregnant, and keeping someone in a study, maintaining them on a placebo dose of LH, I think would have run into issues of feasibility that would have probably made the study undoable in my opinion, but you have others on the panel who I think can comment on that.

DR. GIUDICE: Yes, Dr. Lipshultz.

DR. LIPSHULTZ: I may have missed this data, but Dr. Santoro was talking about how much you like the ability to vary your FSH and keep your LH steady.

In the rollover group, I am assuming then that the LH was kept at 75 and the FSH varied. What was the dose that you needed then to achieve those pregnancies with your FSH? Do we have that?

MS. WILLIAMSON JOYCE: Yes, we do, and your first assumption is correct, the LH dose was kept constant and the FSH dose was allowed to vary.

DR. LIPSHULTZ: What were the doses that achieved efficacy, were they down to 25, because Dr. Santoro suggested that she often has to go down as low as 25 in these women?

MS. WILLIAMSON JOYCE: I am sorry, I want to clarify that. I am quite certain that what Dr. Santoro was saying, that the desire was to reduce the FSH dose.

DR. LIPSHULTZ: Right, the FSH.

MS. WILLIAMSON JOYCE: Yes.

DR. LIPSHULTZ: So, what was the FSH used in that rollover group?

MS. WILLIAMSON JOYCE: Dr. Lammers.

DR. LAMMERS: You are correct that the dose of FSH changed. It was part of the design of the study.

If I can have the slide on, please.

[Slide.]

This table summarizes the FSH dosing, as you requested, Dr. Lipshultz, in the 54 cycles included in this rollover study, and you can look here.

The average daily dose, if we divide it into 150 or even lower than 150, more than 150, you can see the number of cycles, that 30 percent that

had a lower dose of 150, 68 percent had follicular development, and 37 or 6 out of 60 of these patients achieved pregnancy.

In the 150 is 30 percent pregnancy rate, 3 out of 10 patients responding. More than 150 dose of FSH, we had a 75 percent follicular development with a 39 percent pregnancy rate, or 11 out of 28.

DR. LIPSHULTZ: Yes, but in that less than 150, that you have to go below 75, because Dr. Santoro was indicating that her problem with the urinary product was that she is stuck with the 75. So, did you go below 75 in this less than 150?

DR. LAMMERS: I think we have that data, but it is not summarized. We have the data, however, we can provide it to you later.

DR. GIUDICE: Dr. Lewis.

DR. LEWIS: Two things. One, it is very difficult to design a trial to treat these patients, and, of course, the way we use gonadotropin in clinical practice is to tailor the dose as much as we can to the individual patient, so I can respect that it is very tough to design a trial to look at what an effective dose would be.

But looking at these data where you do get a delayed response with 25 in some patients, it

does beg the question of whether 50 would work. I mean I understand it is hard and these are rare patients, and this is expensive, but it is also hard to make a judgment about what the effective dose is.

The second comment I would make is that there is another way to titrate the LH dosage, and that is with hCG. Clearly, that would be off-label, but there are some trials using fixed doses of FSH and then small, very small doses of hCG, which acts just like LH and has a longer half-life, much less expensive, and, of course, there is a recombinant formulation available.

DR. GIUDICE: Does the sponsor want to reply to either of those comments?

MS. WILLIAMSON JOYCE: I wasn't sure if you had a question for us or if you were just commenting on behalf of the committee.

DR. GIUDICE: It has certainly been very instructive to think of alternative strategies for alternative protocols, but I would like to remind the committee that our responsibility today is to look at the protocol and the protocols that have already been conducted and to analyze the data that have been provided.

Before we break, there are two burning questions over here from Dr. Macones and Dr. Crockett, so please go ahead.

DR. MACONES: This is really more of a comment than a question, and it is following up Dr. Toner's questions earlier.

Dr. Lammers presented I think a very pivotal slide which compared the FDA analysis to the Serono analysis. In the analysis after removing the people who were at risk for OHSS, the difference really came down to one patient who Serono defined as being a success because she achieved a pregnancy, FDA did not.

I think what is interesting, at least as I saw that slide quickly, was that the estradiol level in that patient was low, and that is why FDA suggested that that was a failure. I think that is consistent with what Dr. Toner was saying, that we think that the LH is really working based on at least partially through an estradiol level, so whether or not you can really count that as a success, again, a chemical pregnancy that is implanting into an endometrium that is not ready, I really question.

So, it is just a comment more than a

question.

MS. WILLIAMSON JOYCE: I just want to note again that that was prospectively defined in the protocol and never an issue in our discussions with the agency until after the NDA was filed.

DR. GIUDICE: I think it is also important to point out that we should be careful about drawing conclusions for the reason why that may not have been a successful pregnancy.

Yes, Dr. Crockett.

DR. CROCKETT: Yes, I have a question concerning the health of the pregnancies. Yesterday, we heard a lot of discussion about aneuploidy and the risk of genetic defects when we superovulate women.

I haven't seen any data in my review on the genetic health of the pregnancies in this trial, any of these trials, so I would like to know from the company about the genetic outcomes, whether they were live births, terminations, or fetal losses, what the genetic abnormality rates were.

MS. WILLIAMSON JOYCE: Yes, we have those data. What would you like to see, the studies specifically, the pivotal trial?

DR. CROCKETT: I would like to see it all.

MS. WILLIAMSON JOYCE: Okay.

DR. GIUDICE: Slide 71, I have been told has the table in it. Then, Dr. Lammers, if you would like to make a comment.

DR. LAMMERS: Have we got Slide 71 on?

[Slide.l]

DR. LAMMERS: This table summarizes, presented the results of all studies included in our Luveris development program, looking at patients seeking pregnancy, going on to clinical pregnancy, going on to live birth, the number of miscarriages, lost to follow-up, and stillbirths.

We do have information, we have tried to obtain information--I will try to show you that in a minute--on the patients who went on to deliver live babies, either the singletons, twins, and triplets that you were referring to.

Can I have the next slide on, please.

[Slide.]

Again, later, it is always difficult to acquire information, however, this is in 6253, where we looked at a patient who had a pregnancy in the 225 IU dose group, and basically, the mother confirmed--this is last available data in May of

2000--that daughter is doing well.

Here, on the 75 IU dose in 6253, also, this patient delivered twins, male and female, and mother confirmed that the children are healthy.

Next slide on, please.

[Slide.]

If you look at Study 21008, we had the placebo in the 75 dose group, we had twins in the placebo, and basically, she delivered two babies, small for age, 25 weeks, and they were small weight and birth weight, and the 75 was a singleton at 38 weeks, a boy, and also relatively lower birth weight.

The next slide.

[Slide.]

We are looking at our bigger study 21415, you can see here that most of these were delivered at the appropriate time. There was a variation between 30 weeks and the highest I think of 42 weeks of pregnancy, most, you can see the weights here. There are a few low for birth weights babies, but it fits with the gestational age, also here with the 30 weeks.

However, the majority of these children are doing well as far as we have--we have tried to

obtain follow-up information as we discussed yesterday, but it provides issues of lost to follow-up, and people also are not willing to provide that kind of information after they concluded the study.

Does that answer your question? We didn't do any genetic studies that you are particularly referring to, as we discussed this morning, because we didn't do any, you know. Most of the information was not available at the time that we did the studies.

DR. CROCKETT: So, am I to assume that in all of the live births that you had in your studies, you don't have any Down's syndrome children that you know about or any other genetic defects that happen in the normal population?

DR. LAMMERS: No, we do not.

DR. GIUDICE: Thank you.

For the committee, you can leave your books here, and the room in the restaurant is still reserved for today, as well. Please, let's reconvene to keep on schedule at 1 o'clock when Dr. Slaughter will give her presentation.

Thank you.

[Whereupon, at 12:35 p.m., the proceedings

were recessed, to be resumed at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:10 p.m.]

DR. GIUDICE: Since the afternoon agenda is quite tight, we are not going to have a formal break, so if people get up to use the facilities, please be aware that no one else is going to be offended by your exit.

I would like to begin right now with introducing Dr. Slaughter, who is the Reproductive Team Leader for the Division of Reproductive and Urologic Drug Products at the FDA. She will be speaking on Luveris: The FDA Perspective.

FDA Presentations

Luveris: The FDA Perspective

DR. SLAUGHTER: Good afternoon. I hope you all had a good lunch even though it was somewhat rushed. As Dr. Guidice said, I, along with Dr. Meaker, will be presenting the FDA perspective on the Luveris Drug Development Program.

[Slide.]

The NDA indication for Luveris was for concomitant administration with recombinant FSH for the induction of ovulation in infertile women with severe LH and FSH deficiency.

This, I might mention was actually a second change in the indication with the original one being for women with LH and FSH deficiency, and as you hear today, the sponsor has now proposed a third indication, that we might change to a third indication.

[Slide.]

The object of the population is women with hypogonadotropic hypogonadism or hypothalamic pituitary failure. The criteria for enrollment in the NDA studies has defined subpopulations of hypogonadotropic hypogonadal women requiring therapy based on serum LH, FSH, and estradiol levels with or without functional evidence of endogenous estrogen.

[Slide.]

Luveris was granted orphan drug designation on October 7, 1994.

[Slide.]

The Orphan Drug Act of 1983 refers to orphan drugs as rare diseases or conditions affecting less than 200,000 persons in the United States. It confers certain marketing exclusivity.

Orphan products receive no preferential treatment in terms of testing and submission

requirements, and face the same safety and effectiveness criteria and review processes as undesignated products.

[Slide.]

As mentioned earlier, the FDA has no concerns with the ultimate safety profile as presented in the NDA, so the presentation today will discuss efficacy only, focusing on population, endpoints, and how these things have changed throughout the drug development process or program, and the power of the Phase III study and the dose.

[Slide.]

My overview of efficacy will cover the primary studies proposed to establish efficacy, FDA requirements to establish efficacy. I will examine the regulatory evaluation of Luveris, focusing on the strength of the evidence, and will summarize the concerns of the FDA, and finally, we will come to the committee with our questions.

[Slide.]

Two identical Phase II dose-finding studies were proposed to the FDA in 1992, when the company met with the FDA in a pre-IND meeting.

One of those proposed studies, U.S. Study 6905, was submitted to the FDA in an IND in 1993.

Annual reports to the IND, beginning in 1996, identified U.S. Study 6905 as the proposed primary study to support an NDA. Remember, initially, there were two identical Phase II dose-finding studies proposed.

Study 6253, the study conducted in Europe, the European Phase II study, was not submitted to the FDA, and, in fact, the FDA was not aware of the data from Study 6253 until we were at the discussions just prior to submission of an NDA.

In 1998, this study, 6253, was proposed as the primary study to support the NDA.

[Slide.]

These studies had different patient populations and efficacy criteria. The U.S. Phase II study submitted to the IND, Study 6905, was open-label. It enrollment criterion was for an LH less than 5, an FSH less than 5, and a negative progesterone challenge test.

This protocol was amended prior to conduct of the study and it changed the population to an LH less than 13.3, the progesterone challenge was replaced with an estradiol less than 60, and there was a change in the FSH requirement.

This, the sponsor did, as you heard

before, based on recommendations from their own consultants.

Finally, the European Phase II Study was also an open-label study. The LH requirement was for a less than 1.2, a negative progesterone challenge test was required, an estradiol level was not required.

Additionally, this European trial enrolled volunteers, not necessarily seeking to become pregnant. The efficacy criterion that were put forth on these Phase II trials was a combined efficacy endpoint taking into consideration follicle size, estradiol on the day of hCG, a mid-luteal progesterone level.

As you see, these efficacy criteria also varied. In Study 6905, an estradiol was to be greater than 200 pg/ml and a mid-luteal progesterone greater than 10 ng/ml. This was changed when the study was amended to make it greater than 160 pg/ml and greater than 7.9 ng/ml, and the European study was 109 pg/ml with the estradiol criterion of the combined endpoint, and a progesterone of 7.9 ng/ml.

[Slide.]

The briefing document for the proposed NDA

was submitted in 1998, and over a period of 1998 to 1999, the FDA reviewed these documents and had numerous discussions with the sponsor.

Two non-identical Phase II studies, 6905 and 6253, were proposed. No statistical hypothesis was set forth for these studies at the outset. These studies were not powered for efficacy.

They used trend tests as confirmatory statistical tools for efficacy assessment. FDA considered at that time, and considers now, that trend tests are exploratory, and not to be used as confirmatory statistical tools.

The result of the European study was significantly different from that of the U.S. study 6905.

[Slide.]

As a result of the FDA sharing its concerns, Serono proposed then to support an NDA with Study 6253, the European Phase II, as primary as opposed to what was identified to us in 1996 and 1997 as 6905 being primary.

[Slide.]

The FDA's conclusion on Study 6253 was that the database was insufficient for filing an NDA. It was composed of 11 patients on 75 IU dose

of Luveris versus 9 patients on placebo.

[Slide.]

The FDA presented two options to the sponsor. One was that we could discuss with an Advisory Committee whether the database for Luveris was sufficient to support an NDA.

[Slide.]

The second option was that the sponsor could conduct a Phase III study. A further recommendation for such a Phase III study was that the sponsor enroll patients with an LH less than 5 and a significant subset with an LH less than 1.2.

The reason for making a recommendation of enrolling subjects with an LH greater than 1.2 was that the labeling could reflect both the population showing efficacy and that for which the product was ineffective if the data did indeed turn out that way.

We have had several discussions on pregnancy in subjects with WHO Type I, and the agency did suggest that it was really interested in pregnancy, however, if the study could not be powered to demonstrate a difference in pregnancy rate, then, ovulation rate, the proposed label indication, should be the primary clinical outcome.

We said that a single treatment cycle, as proposed by the sponsor, would be adequate to demonstrate efficacy regarding ovulation rate.

[Slide.]

In 1999, the sponsor submitted its Phase III protocol. The population in that Phase III protocol was an LH less than 1.2, the same as Study 6253, with an E2 less than 60 pg/ml. It was proposed to be a single dose study and study follicular development as the primary clinical outcome.

Serono's cover letter stated that a review of Serono data indicates that use of ovulation rates as a primary endpoint would be burdensome since some patients would be canceled for the risk of OHSS, and will not reach ovulation.

[Slide.]

The FDA comments to the Phase III protocol were that the drug development program to date had not demonstrated dose responsiveness, that the protocol proposed only a single 75 IU dose. It included a historical control, and the population studied was different from the previous FDA recommendation to include a population with an LH less than 5 with a significant subset less than 1.2.

[Slide.]

FDA's recommendation on that protocol was that the sponsor should demonstrate dose responsiveness, should determine the lowest effective dose in Phase III, or alternatively, conduct a separate Phase II trial.

FDA further stated that a single dose may be an issue that affects the outcome of the review recommendation and that we might not have determined the lowest effective dose.

We further recommended a placebo arm, and not historical data as the control.

[Slide.]

Further recommendations were that the ultrasonographer and patient be blinded, and if the sponsor was not going to take our recommendation to use ovulation rate as determined only by the progesterone, then, we had some comments on the criteria for their combination primary endpoint. We suggested an estradiol of 200 pg/ml and a progesterone level of 10 ng/ml.

We felt that that was more in keeping with estradiol levels attained by a mature follicle in a normal menstrual cycle.

[Slide.]

The NDA was received on May 1st, 2001. As I said, the indication was for concomitant administration with recombinant human FSH for the induction of ovulation in infertile women with severe LH and FSH deficiency.

The NDA was supported by one Phase III trial, Study 21008, and two, non-identical Phase II does-finding studies.

[Slide.]

On March 1st, 2002, the NDA received a non-approvable decision by the Division of Reproductive and Urologic Drug Products.

[Slide.]

I am going to give an overview, a little more in depth, of the three studies supporting the NDA, as well as the extension study 21008. Again, some of this will be a repeat of what Serono has already shown you.

[Slide.]

U.S. Phase II Study 6905 and European Phase II Study 6253 had objectives to determine the need for LH and the minimum effective dose for ovulation induction. The FDA review determined that the lowest effective dose had not been determined.

U.S. Phase III had an objective to confirm the efficacy and safety of the 75 IU dose of Luveris. The FDA review was that the 75 IU dose of Luveris was not effective.

[Slide.]

This slide now is just an extension of the previous slide that I showed to include the U.S. Phase III trial, and just so that it is very clear the Study 6905, the U.S. Phase II open-label, the European Phase II open label, and finally, the Phase III double-blind study had different enrollment criteria.

The European Phase II and the U.S. Phase II were the same. The efficacy criteria did differ between the U.S. Phase II studies and the European Phase II and the U.S. Phase III trial.

[Slide.]

Whereas you have already heard, one of the major discrepant point of views that significantly influenced the outcome of the review was the issue of how to account for cycles canceled to avoid ovarian overstimulation syndrome.

The FDA believe that cycles should not be considered as a treatment success for the purpose of evaluating the efficacy for ovulation induction

and pregnancy.

We believe that cycles canceled to avoid the risk of OHSS, a pharmacologic adverse event, is not a surrogate for pregnancy.

[Slide.]

I won't go over this again because I think this was presented by Serono, but FDA believes that the appropriate way to account for cycle cancellations is to plan for and prospectively adjust the sample size.

[Slide.]

Study 21415, the extension study, was a non-randomized, open-label extension of Study 21008 that included 31 patients with an LH of 1.2, who are treated in Study 21008, who had not conceived.

The primary objective was provide additional data on follicular development and safety of the treatment with the 75 IU dose of Luveris.

[Slide.]

Next, I would like to say a little bit about what the FDA considers as substantial evidence.

[Slide.]

Congress, in the Federal Food, Drug, and

Cosmetic Act of 1962, put forth that the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations. Historically, these were interpreted by the FDA to mean more than one.

The Modernization Act of 1997 stated the data from one adequate and well-controlled clinical investigation and confirmatory evidence are sufficient to establish effectiveness and FDA may consider such data and evidence to constitute substantial evidence.

[Slide.]

Working on these statutes, the FDA put forth a guidance for industry. That guidance says reliance on a single study "whether alone or with substantiation from related trial data leaves little room for study imperfections or contradictory nonsupportive information."

The results of the two, Phase II trials are contradictory. The results of the Phase III trial is not robust. It relies on the results of a single patient.

Also, the guidance puts forth that a single study should be limited to where confirmation would be practically or ethically

impossible.

It is both practical with an extended use of patient accrual and ethical to provide substantial evidence for Luveris in the treatment of women with hypogonadotropic hypogonadism.

Next, I will turn the mike over to Ms. Meaker, who will present the statistics.

MS. MEAKER: Hi. My name is Kate Meaker and I am the statistical reviewer for this NDA.

[Slide.]

First, I will be presenting the FDA's re-analysis of the three main clinical trials, and then I will discuss the agency's conclusion that these trials lack sufficient evidence for efficacy.

[Slide.]

The main issues, as Dr. Slaughter already explained, are the classification of subjects whose cycles were canceled due to risk of OHSS, and secondly, the concerns that the results of these studies are not robust.

[Slide.]

I will be covering the same three main studies that Dr. Slaughter has already described.

[Slide.]

Some background on the Phase II studies.

The planned analyses for these studies were trend tests. This type of test is appropriate for dose-finding studies, which was the goal of the two, Phase II trials.

Weights are assigned to each dose group prior to unblinding, and typically, the weights will reflect the anticipated dose response, such as a linear response.

[Slide.]

Our concerns about the sponsor's trend test analyses are these weights were not pre-specified, and when the results were first presented to the agency, we were told that the weights were selected after unblinding. This creates bias in choosing weights which show the greatest support.

[Slide.]

An additional concern was that the 75 IU dose group and the 225 IU dose group received the same weights, and the actual weights applied were placebo received minus 2, 25 IU dose received a weight of zero, and then the 75 and 225 IU dose received the weight of 1. So, in essence, this test treats anyone who received 75 or higher as having the same dose.

[Slide.]

Now, the results of these studies, and for each of the three main studies, I will be presenting the same analysis table. The first line will be the sponsor's analysis as presented in the NDA, and this includes OHSS, risk for OHSS as a treatment success for follicular development, and then the second line will be my re-analysis, which will include risk of OHSS as a treatment failure.

Here, the endpoint that we are looking at is percent success on follicular development.

[Slide.]

So, in Study 6905, the sponsor's analysis, as they already presented, the trend test was not significant. One other point, in the process of my review, of the agency's review of this NDA, the question came up can any of these studies stand alone to support the efficacy of the 75 IU dose.

[Slide.]

So, to address that question, in my re-analysis, I did a direct comparison of the 75 IU dose group to the placebo group, and in doing that, I used a Fisher's Exact Test.

For this study, comparing the 7 out of 11 to the 5 out of 11, Fisher's Exact Test is not

statistically significantly different. So, in conclusion, when OHSS risk is a treatment failure, actually, in both of these analyses for 6905, there was no statistical difference.

[Slide.]

Moving on to the second Phase II study 6253, again, sponsor's analysis. This was presented this morning. The trend test had a significant p value of 0.004. The other thing that was presented this morning was the sponsor compared this 7 out of 11 to the 1 out of 9 in head-to-head comparison, and showed a p value of 0.02. Again, that was with OHSS risk as a treatment success.

[Slide.]

When this is reclassified in my analysis, the comparison of the 75 IU group to placebo shows no statistically significant difference.

[Slide.]

Finally, moving on to the Phase III trial, this is a single Phase III trial. It had just two groups, Luveris and placebo. The plan comparison was a head-to-head comparison using a Fisher's Exact Test.

Just to clarify, this was the analysis that was presented in the NDA. The sponsor did an

evaluable analysis, they excluded three subjects from their analysis.

Now, what was presented this morning, just to clarify the differences in what you are seeing in the package, this morning the sponsor presented an intent-to-treat. So, their denominators this morning were 26 in Luveris and 13 in placebo. That is the same intent-to-treat population that I used in mine.

[Slide.]

In doing a Fisher's Exact Test comparison, the p value for mine is 0.063, and as you have heard, there is a single subject in the Luveris group. The sponsor's analysis will show 11 out of 26 as being a treatment success here. There is a single subject where there is disagreement between the agency and the sponsor about the clinical, I guess it's the chemical pregnancy.

So, this raises additional concerns about the robustness if the interpretation of this single Phase III study hinges on the classification of a single subject.

So, again, when OHSS risk is considered a treatment failure, the single Phase III study does not have sufficient evidence to show efficacy for

the 75 IU dose.

[Slide.]

This slide is to summarize the results of these three individual trials, and what I am showing you is the odds ratio and the 95 percent confidence interval. Now, the odds ratio shows the chance of having success, chance of follicular development in the 75 IU dose group versus the placebo group. The 95 percent confidence interval corresponds to the test at alpha .05.

Now, the vertical line at the value of 1 here represents the odds ratio where the chance of treatment success in the placebo group is the same as treatment success in the Luveris group. All three of these confidence intervals, the lower bound is less than 1, so none of these trials can rule out the possibility of equal chance of getting pregnant or equal chance of follicular development on placebo as on Luveris.

[Slide.]

Of interest to the agency's medical officers was ovulation rate. This was the desired indication was ovulation induction. FDA requested that the sponsor use this as a primary endpoint, as Dr. Slaughter already discussed, and ovulation rate

was to be determined by progesterone levels.

The sponsor chose to use follicular development instead as the primary endpoint, and this was shown as the secondary endpoint.

[Slide.]

This slide shows the results of ovulation rate for each of the three studies. Now, you will notice in the 6905, the progesterone level was slightly higher than in the other two to be classified as a success for ovulation, but in all three studies, a head-to-head comparison, there is no statistically significant difference between Luveris 75 and placebo for ovulation rate.

[Slide.]

So, in summary, these three studies, when we try to answer the question can any of them stand alone, looking at the primary endpoints with OHSS risk as the treatment failure, there is insufficient evidence and also looking at the additional endpoint that was of interest to the medical officers, ovulation rate, the same conclusion. None of these studies can stand alone to support that efficacy.

Now, I will return it to Dr. Slaughter.

DR. SLAUGHTER: Let me say that FDA agrees

that in some population of hypogonadotropic hypogonadal women, LH will be necessary.

[Slide.]

Our concerns have been that we were left with, at the end of this review, were the appropriate subpopulation of hypogonadotropic hypogonadal women that would benefit from therapy with exogenous LH; that the correct surrogate for pregnancy was not chosen in this instance.

[Slide.]

Finally, in the appropriate population, the lowest effective dose.

[Slide.]

As you have heard earlier, there are alternative treatments, intravenous gonadotropin hormone releasing hormone is not currently marketed, and the menotropins have never been presented to the agency for this indication, so they would be used off label.

I will proceed with our questions for the committee.

No. 1. Can subpopulations of hypogonadotropic hypogonadal women be identified solely by serum hormone including LH, FSH, and estradiol levels? This is in addition to the

physical examination, et cetera.

If you do not agree, what additional markers should be attained? Should it be demonstration of withdrawal bleeding upon progestin challenge, DNA markers, or other clinically significant markers?

If you agree that subpopulations can be identified on the basis of hormone levels, were the appropriate subpopulations studied in 6905, 6253, and 21008?

No. 2. Was a placebo-controlled trial the appropriate trial design to demonstrate efficacy? If you disagree, should an active comparator trial be considered?

No. 3. Should multiple cycles be considered for evaluation? Is there a priming effect of the first treatment cycle?

No. 4. Was it appropriate to use a surrogate endpoint for pregnancy? We have talked this over several times. In this case, follicular development, however, in this study of hypogonadotropic hypogonadal women seeking pregnancy?

If you do not agree, should the studies have evaluated clinical pregnancy or live birth?

If you agree, which surrogate endpoints should have been used? A single mid-luteal progesterone? Multiple mid-luteal progesterone levels? Or other surrogates?

Should cycle cancellation to avoid OHSS be used as a surrogate for pregnancy?

No. 5. Is the data sufficient to establish efficacy for ovulation induction?

No. 6. If additional clinical studies are to be recommended, what type of study should the Division request in order to provide sufficient evidence of efficacy?

Should additional studies evaluate doses lower than 75 IU?

Finally, I would like to close in thanking the committee for your deliberations over the two days. These are very important issues that the Division has struggled with, and we very much appreciate all of your input.

I would also like to thank the following people: Dr. Ridgely Bennett, who is in the audience. He is the medical officer who has worked on the drug products for infertility for over the last 30 years, and we owe him a tremendous debt.

I would also like to thank Dr. Audrey

Gassman, Dr. Barbara Wesley, and Ms. Dornette Spell-Lesane for all of their help in putting together this presentation.

I would like to thank Drs. Griebel, Shames, Houn, and Jenkins for all of their valuable comments during this process of presenting before the committee.

Thank you.

DR. GIUDICE: Thank you, Dr. Slaughter.

I would like to open this discussion for some questions from the committee to Dr. Slaughter specifically about the issues that she has discussed, and I would like to begin the questioning by at least recounting as someone who was naive to these data and a first time around, and I would like to hear comments also from other committee members.

We seem to have essentially two sides of the story. There are two different statistical analyses, there are comments that the FDA gave favorable views and yet within a few months there was an unfavorable letter.

There is an issue that has been made of not having identical trials from the beginning or Phase II studies from the beginning. What that

exactly means to the committee or to the FDA, I for one am not completely clear.

There is a Phase II trial that was conducted in Europe that--and pardon me for using the word "clearly," Dr. Emerson--but it seemed pretty clear to my eye that there was a dose-dependent, statistically significant change with recombinant LH.

There are comments about the 6905 study not being equivalent and both trials not being equivalent to the 6253. Very little discussion has been addressed to the subset of severely LH-deficient patients in the 6905, the data of which again to my eye in reviewing the data seemed very comparable to the 6253.

I can go and on. These are the issues that when I have gone through the data head-on, came to my pen to paper. An additional issue was brought up today, and that has to do with the pivotal patient of an estradiol of 106 versus 109, and again no discussion has been made with regard to had we re-assayed that patient sample, or had drawn her blood within five minutes, would we have gotten 110 nanograms per ml for an E2 or perhaps a 100.

At least as I understand biology, you don't usually get pregnant unless you have follicle development. So, these are very serious issues that, as I have gone through the data, these have come to my mind, and as a group, I would like for you to let me know if these are on target with your thinking and how we can advise the FDA with regard to this particular product proposed by this sponsor.

With that as a background, because I do want people's juices to be flowing here, I really want the brains to be thinking especially postprandially. There are a number of questions, and as we look at the subquestions, we need sufficient time to be able to discuss these, because some of them are very subtle and some of them I think are going to require a lot more attention.

With that as a background, I would like to open the discussion for questions for Dr. Slaughter.

Yes, Dr. Tulman.

Questions from the Committee

DR. TULMAN: I am asking this and it might be a bit broader rather than narrow. When the

sponsor applied for orphan status because of the rarity of the condition, and has spent, and the FDA has spent, a considerable amount of time looking at a drug that, by all accounts is for the very rare patient, the 1 in 18,000 perhaps a tertiary care center.

Clearly, there is in the background another agenda that may be at operation here that I think must be put on the table, and that is the FDA approves a drug for a very set purpose, for a set population that you have the evidence or may or may not have the evidence as we are discussing.

The reality is if a drug were to be approved and it goes out to market and it's available for prescription by licensed people who can prescribe, and we all know there is much off-label use, which is not what the FDA approved it for, and in this particular case, there is the potential that the off-label use may outweigh the on-label use by a ratio of 18,000 to 1, which I am not sure how it works out with all our other medications out there, but it seems to me that is a pretty big off-label use potential.

Of all of the trials that have been shown to us, the only one that might give us a hint were

this drug to be approved and were this drug to be then used off label, is the 6905, the one that was done in the United States, of which several of the women in that study were not meeting the LH requirement of less than 1.2, but did go up to the median level, essentially a normal FSH and LH.

There was no breakdown, but doing some calculations on my own, trying to capture that population that was greater than 1.2 in that trial, when you looked at the differences in pregnancy rates, in clinical pregnancy rates, it came out to, for a sample of those 25 women, it came out to 4 in the 75 or 225 dosage, and 5 in the zero or 25, or essentially no difference by any statistical means one could imagine doing.

I know that we are a very focused hearing, and we are focused on this particular population, and somehow we have a gigantic elephant in the room. We have the 17,999 other women as opposed to the other 1 woman with this condition being discussed, and I guess I would like to hear some comments about how we can make a decision for something that the reality in the future may turn out to be very different on the use of this drug.

I guess it wasn't just directed to the

FDA.

DR. SLAUGHTER: Thank you.

DR. TULMAN: It was directed to all of my other colleagues in the room.

DR. SLAUGHTER: I think that I cannot comment about any future or other indications for this drug, so I guess I would like to throw it out to the committee to discuss.

DR. GIUDICE: I would like to comment. When we look at the indication--and I will read it if I can find it amongst all this paper--it is indicated for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency defined by less than 1.2 IUs per liter.

The purpose of this committee is to evaluate the data at hand for the indication proposed. So, I believe that we should focus our--because we don't know, just as many other drugs are used off label--we don't know other applications at this point for the use of this drug, nor really is that our charge to address that.

My understanding of our charge is to advise the committee regarding this particular

indication for this particular NDA. Unless someone wants to have some additional comment, Dr. Stanford, and I would appreciate it if we can keep this brief because we have a number of other very important questions that the FDA has requested that we address.

DR. STANFORD: All I wanted to say is I want to clarify what is the indication we are asked to consider. There have been three different indications. There was one presented in the packets and then the one presented here is different.

The ones you are asking us in the question, I think that is a pivotal question and may affect our vote, it may affect which way we vote.

Is the indication--you asked No. 5--are the data sufficient to establish efficacy for ovulation induction, whereas, the presentation from Serono this morning is proposing an indication for follicular development. Those are different things.

So, what are we being asked to consider?

DR. SLAUGHTER: I think Serono is offering up an alternative indication. The indication in

the NDA was for induction of ovulation.

DR. STANFORD: Are we sort of open to say we will vote no on one and yes on one, are you just asking us to vote on this one? I am just trying to establish the parameters of what we are being asked to address.

DR. SHAMES: We can certainly discuss everything, but technically, it was the ovulation induction indication that we ultimately did not approve, and that is what we need the help on. You can discuss the other issues also, but technically, it's that particular NDA having to do with ovulation induction that we need the answer.

Question 5 is the actual question regarding that.

DR. STANFORD: So, we would vote on Question 5 and then make any other comments that you might take into advisement for anything else.

DR. SHAMES: Right. I want to make one other comment about the off label, et cetera. The other way to look at it is we are looking at this, the information before us, and if reproductive endocrinologists think it would be really nice to have, you know, some LH to fool around with, and we were really nice and we said, okay, we could have

this, the truth is we are, by law and by regulation, required to approve a drug based on what Dr. Slaughter showed you, substantial evidence.

It is fairly well defined as what is substantial evidence, and it has to do with the number of trials and the supportive evidence. So, the other way to look at this, you have to sort of take your way, in a sense, out of the total big picture and focus on not only the clinical evidence or the trial evidence, which you would look at as academicians or practitioners, but also on our regulatory charge, which is a certain legal standard of having substantial evidence which has a real meaning to it.

So, that is why Dr. Slaughter reviewed with you what that was.

DR. GIUDICE: Dr. Keefe.

DR. KEEFE: We are going to be making decisions based on whether or not there is or is not substantial evidence to support the IND, and I am wondering if, from the perspective of the FDA, does the fact that this is a deficiency syndrome, that this is as close as you can get to the natural product, way into it, for example, if this was a

new form of insulin, does it change the weight of the evidence required to tip the balance in one direction or another.

DR. SLAUGHTER: I think that I put this on the slide. It really doesn't influence the weight of the evidence. We have to consider these drugs for these orphan indications in the same manner that we would consider other drugs.

DR. SHAMES: There is a reason we are replacing this, and we have to decide. The endpoint here is the reason we are replacing it to attain pregnancy. I mean there may be a lot of things that people are deficient in as you get older, whatever it is, but to approve something, there has to be an endpoint that has clinical meaning, not just replacing the particular deficiency.

DR. GIUDICE: Dr. Rice.

DR. RICE: I guess I am just not clear because what Serono presented us this morning, the second slide says they are looking for indication for stimulation of follicular development, and apparently they amended their NDA on August the 21st, 2003, which you present to us is an NDA indication for ovulation induction.

So, which endpoint are we going to make a decision on, ovulation induction or follicular development? In other words, do they get to change midstream their decision or amend the NDA and was that accepted by the FDA?

DR. SLAUGHTER: Our decision was based on ovulation induction. We did not accept the amendment to change it to follicular development.

DR. RICE: So, today, we are making a decision based on ovulation induction, not follicular development?

DR. SLAUGHTER: Yes.

MS. WILLIAMSON JOYCE: Excuse me. May I comment on that? I want to make it clear that the NDA amendment, the proposal to create an indication that was more clearly closely aligned to the clinical development program, starting back more than 10 years, and also to make it consistent with the indication that is currently approved in over 46 countries.

Now, that indication, the proposal to amend that indication was provided to the agency in a document in December of 2002 with hopes that we could get to the part of our discussion where it might be possible, however, given the fact that the

matter was being brought before an advisory committee, we have not to date entered into any discussions concerning the label.

We are proposing this indication because we feel it is appropriate based on the clinical studies that we have conducted, and today was the first moment that we were told that the amended indication was not accepted.

DR. GIUDICE: Dr. Hager.

DR. HAGER: That was my question.

DR. GIUDICE: Dr. Lipshultz.

DR. LIPSHULTZ: I have a question for Dr. Slaughter. We are talking about this one patient, and Dr. Guidice mentioned, well, if we drew the blood again, perhaps it would be different.

I mean if that one patient is so significant in this decisionmaking, then, I am concerned about the depth of the data that we are discussing. How important is this one patient?

DR. SLAUGHTER: If you eliminate women, if you do not count as successes women whose cycles were canceled for the risk of OHSS, the data is swayed from a significant p value to a non-significant p value on the basis of that one patient. So, the one patient really influences the

outcome of this study.

DR. LIPSHULTZ: Because the sponsor has said that either way you look at the data, with or without the canceled cycles, it still is statistically significant, but you are saying that if we cancel the one patient out, then, it does change the data.

DR. SLAUGHTER: If you take that one patient along with patients whose cycles were canceled for the risk of OHSS, then, yes, it does influence the data.

I just wanted to respond to some of the points that you raised initially. One is that I presented the business about which studies were to support the NDA only to give you some historical perspective and that things were not clear-cut from the onset, that we were presented with the proposal for different studies to support the NDA over the 10-year review process.

I think we did discuss the single patient. I just wanted to make a little comment about the favorable response, and it's not to get into a he said-she said situation, but I just want to put that in perspective.

The comment that Serono has put forth

about the favorability of the study was made by me, and I was commenting at the level of the pre-NDA meeting, that the sponsor had done the type of study, meaning double-blinded, placebo-controlled study that I had asked for, and that was favorable.

However, left out of that comment was that we could not even tell them at that time whether we would accept that NDA for filing. That comment was in no way made to suggest that they would ultimately receive a favorable outcome after the review of their NDA.

DR. GIUDICE: Thank you. I would like to have two quick comments and then we need to go to the open public hearing, and then we will go directly to the questions.

Dr. Crockett and then Dr. Rice.

DR. CROCKETT: I actually have a question to address to Dr. Emerson, our statistician. In reviewing Dr. Meaker's statistical analysis, there seems to be significant difference regarding the statistical analyses applied to the data both on the follicular development and the ovulation rates.

In her presentation of the data, neither the follicular development nor the ovulation rates were statistically different between the Luveris

and the placebo, and I just wondered if you had a comment concerning the correct application of the statistical methods used.

DR. EMERSON: There were differences in the statistics being presented, the types of things that you are looking for. So, first, the issue is doing a test for trends versus the pairwise comparison, and obviously, there is a multiple comparison issue, if you let me do enough statistics, I will eventually find out something that is significant.

So, this prespecification question is very, very important when you are doing a test for trend, prespecifying the weights is very, very important, so there is a lot of issues there that you can say sure, they plugged it into the computer, and the computer gave it the correct p values subject to the differences in the definition of failures and dealing with the one patient.

But the issues of the weighting and whether it is prespecified and whether that would be then the credible evidence is one that has to go in the study design, because you have to be very certain that you aren't given too many chances to be right.

I would say that everything looks like it is appropriate if there wasn't an element of dredging through the data until you got the result that you wanted.

DR. GIUDICE: Dr. Rice.

DR. RICE: This is a comment and I guess I may want a response, but I am concerned about this history of this changing of the NDA indication and I just want to know is there some precedent for this, that before a pharmaceutical company comes before us that they can have changed the indication, the endpoint that was going to be evaluated, is there any history of that, and I guess I am concerned about what you just said was that you changed the indication after you looked at the data.

Did I misunderstand that, after it has been approved in the European study, what did you say?

MS. WILLIAMSON JOYCE: Yes. First of all, I want to make clear that there has been no change in the endpoint, the endpoint has been consistently applied in the pivotal study and in the previous studies. There has been no change in the endpoint.

DR. RICE: So, ovulation induction versus

follicular development?

MS. WILLIAMSON JOYCE: The endpoint has always been follicular development as provided by Dr. Lammers and the sharing of our data, that has always been set, follicular development. What we did, when the NDA went in, the wording of the indication that was submitted was broad and similar to that of other products that had been approved in gonadotropin treatment therapies for OI.

It was clear as we looked at this that that was an overly broad indication.

DR. RICE: Which was an overly broad indication?

MS. WILLIAMSON JOYCE: The initial indication submitted in April of 2001, ovulation induction. So, there was a disconnect between the indication that was included in the original NDA--

DR. RICE: Ovulation induction.

MS. WILLIAMSON JOYCE: Ovulation induction--I want to clarify this, it was stimulation of follicular development and ovulation induction. All we did was remove the term "ovulation induction" because we felt follicular development, stimulation of follicular development was what we had studied. That was our endpoint,

and in changing that indication, we combined, we made consistent the endpoint and the proposed indication, which is also approved in the other countries in the same terminology. So, I hope that clarifies what we did. No?

DR. RICE: No.

DR. SLAUGHTER: Just one comment also. That indication was taken word for word from the label that was submitted by Serono with the NDA application.

MS. WILLIAMSON JOYCE: Yes, it was, I agree.

DR. GIUDICE: Can we be very clear, rather than using "it" or "they," so specifically say either follicular development, follicular development and ovulation, and ovulation induction as we discuss these, because it's a very good point.

Dr. Lipshultz, your question was?

DR. LIPSHULTZ: Could you please, as chairperson, restate what was said, because I did not understand. Did you understand?

DR. GIUDICE: What I understood was that the original indication was for follicular development and ovulation induction, and that the

outcome was follicular development, and to make the outcome consistent with the indication, they dropped the words "ovulation induction."

Is that correct?

MS. WILLIAMSON JOYCE: Yes.

DR. SLAUGHTER: After the NDA, after the NDA was submitted.

DR. RICE: So, they dropped it after they looked at the data, correct, which was what I said, you dropped it after--okay, you didn't drop it after you looked at the data.

MS. WILLIAMSON JOYCE: I think we are getting into semantics. The words ovulation induction were proposed to be removed in the amended indication, but follicular development in the indication, which has always been in the indication, and has always been the endpoint, are consistent. That has not changed.

DR. GIUDICE: I would like to remind the committee that the criteria for follicular development, if progesterone, mid-luteal progesterone is one of the sub-criteria, that is almost implicit that there has been ovulation, so you are correct that there is a bit of an issue of semantics here.

Certainly follicular development can occur, and you may not allow ovulation to happen, but with the criteria that were used in the composite, progesterone was one of the endpoints.

DR. RICE: But I think one thing that is somewhat clear to me is that they canceled patients, so you didn't get to ovulation induction, so you never got a progesterone level. So, it was to their favor to use follicular development, because they didn't give those patients the hCG to ever answer the question of ovulation induction, so that is why the semantics makes a difference.

DR. GIUDICE: Well, it does and it doesn't, and I will get to you in just one second, because if one is looking at the pharmacologic endpoint of the action of LH, it is truly not follicular growth, but it is steroidogenesis, and that I think has been--I won't say clearly shown, but we can discuss that elsewhere--but the endpoint for the action of LH had one not canceled cycles because of the risk of OHSS, would have been for ovulation.

It's just on an ethical basis and by the criteria for cycle cancellation, and that's the reason that those patients were not included, but

had one just decided, well, let's take a cutoff of 5,000, then, we would have had evidence of ovulation induction.

So, the pharmacologic action of LH was clearly proven in those patients who were excluded.

DR. RICE: I will only say this. We are talking semantics, and we are talking about one patient making a difference of some statistical difference, but that one patient that we are talking about, when Dr. Macones asked the question what was that estradiol level in that patient who ended up getting pregnant from this "chemical" pregnancy, my understanding was that estradiol level was low.

DR. GIUDICE: It was 106.

DR. RICE: It was under the threshold, so that is your indication for LH action, that estradiol. So, there are some semantics there that raise the question. I just think that we need to be clear about what we are going to discuss, what we are going to vote on, and that is whether or not the drug is looked at for ovulation induction as the endpoint versus follicular development, and that is what I would like clarification on, and I want to make sure that we all understand as a

committee, either it's acceptable that they could drop the wording of the initial indication or they can't, so we just need to know what to vote on as a committee, because I know I can look at the data and assess it for what I think it shows once I know what the question is.

DR. GIUDICE: Dr. Keefe.

DR. KEEFE: It seems to me the pivotal patients are those who had OHSS and never got a chance to have a progesterone that is elevated, which brings us back to Dr. Toner's point earlier, which is whether or not they had adequate estradiol levels.

So, from my understanding of the data, if you include all those who were canceled for OHSS in the group, they will have significance, but if you exclude them, they don't, but the question is if you partition them into those who had adequate levels of estrogen above the cutoff and those that didn't, where does that leave us? Does that put that one patient who is defined as pregnant as the make or break piece of data?

MS. WILLIAMSON JOYCE: Excuse me for just interrupting. I want to make it clear that these patients were not canceled due to OHSS.

DR. KEEFE: I am sorry, the potential for OHSS risk.

DR. GIUDICE: I think we need to move on. We will continue this discussion essentially as we go through the individual questions, so this certainly has provided an excellent base for that.

Open Public Hearing

I would like to open the open public hearing and I need to read a statement by the FDA.

Both the FDA and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session in the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your

attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I understand that we have three individuals who would like to make a statement. Would you please raise your hands. May I have the person who is walking towards the center come first.

MS. KRAMER: Thank you, Chairwoman Guidice and members of the committee. My name is Erin Kramer. I am here to represent Resolve, the National Infertility Association, and I am a consultant to Resolve.

Resolve has been for 30 years providing compassionate support and information to those individuals who are touched by infertility, and Resolve works to increase public awareness of infertility issues and the family building options available to those individuals.

Resolve appreciates the important work of

the agency and this panel, and the careful thought and consideration that must accompany the approval of any new drug.

For the sake of disclosure, the corporate sponsor of the product discussed here today has been a supporter of Resolve's work. I do want to also make clear that I do not have a medical or a clinical background, so I cannot comment on the specific merits of any new product, but I do have an important viewpoint to impart and that is of the patient.

Infertility, receiving that diagnosis is devastating. According to the American Psychological Association's National Task Force on Women and Depression, 40 percent of women in one study identified the inability to conceive as the most upsetting experience of their lives.

Certainly for individuals for whom treatment is not available, that depression would be magnified.

We understand that there is a patient population for whom there is not treatment currently available. Of course, those are the individuals we have talked about today, those who are profoundly LH deficient, and while, of course,

this is a rare patient population and certainly one very difficult to study, we encourage the panel to think about the human toll, of the decisionmaking that goes into the process of identifying and looking at the research.

These women deserve to have treatment that is both safe and effective in the investigational setting and treatment that is specific to their infertility problem. We understand that this treatment is available in European markets and that patients are benefitting there.

While there are numerous factors that go into contributing to the success of treatment and pregnancy in the end, the passage of time and the delay of treatment is a very key component of that success, and 10 years of investigational study is a long time and too long for many patients who are waiting for a family to love and an answer to their medical problem.

The research overwhelmingly is paid for by patients. There is very little federal funding into infertility research, so it is the patients themselves and private companies who are willing to invest the time and money into cures.

We encourage the panel to help assure

timely availability and access to new pharmaceutical products that will be for all infertile patients.

Thank you.

DR. GIUDICE: Thank you for your comments.

MS. MADSEN: Hello. Thank you for having me here today and giving me some of your time. My name is Pamela Madsen and I am the Executive Director and the founder of the American Infertility Association.

I am supposed to disclose. Serono does give the American Infertility Association some funding for educational activities, as well as other people here in the room, Ferring Pharmaceuticals and Organon, and nobody paid for my travel.

I came here today because some patients asked me to come. Those are those orphan patients that we have discussed, not those 17,000, for which there are products available to treat their infertility, but this very, very small group of orphan patients.

While those numbers, 2,000 to 5,000 patients, when you are in the medical practice, seem very, very small. When you are a part of that

couple that is your whole world, so we are talking about somewhere between 2,500 worlds, lives, couples, who are looking to have a baby, and these hypo/hypo women do not have a product that is designated to treat just them.

And how do we measure success? I keep hearing that today over and over again. If I am anovulatory, if I can't ovulate, if I don't get my period, I may measure success in the ability to buy a box of tampons, that's success. If I don't ovulate, follicular development is a success of that drug. Ultimately, if I want to have a child, this drug may help me obtain that final goal.

But there may be lots of different successes for that patient along the way outside of that take-home baby, and I don't think that we should demean that at all, because if you are a woman who doesn't menstruate, menstruation is a victory.

I hope that you will consider those women who were canceled. Again, I am not a doctor, but I know a little bit, and I know lots and lots of patients on lots of different medications who get canceled because of hyperstimulation. As a patient advocate, that tells me something is working, I am

ovulating, I am making a lot of eggs. I am doing something, and the doctor is concerned that I am going to get sick if they don't cancel my cycle.

So, some physicians made some very key decisions to protect my health as a volunteer or participant in the study, but it was working, and I think that patients in the United States should have the same access to care as we are hearing this patients have in other countries.

So, again, let's look at the measure of success for the infertile couple, for the infertile woman, for the woman who is struggling with this. I think it sounds like this drug is working.

Thank you.

DR. GIUDICE: Thank you for your comments.

The last person, please.

DR. SHOHAM: Ladies and gentlemen, my name is Dr. Shoham. I am practicing medicine in Israel. I am the Director of the Infertility Clinic and Kaplan Hospital. I came from Tel Aviv yesterday night in order to participate in this discussion, which I think is highly interesting.

We gain a lot of interest and we need a lot of research in this unique group of patients. Actually, I was involved in Phase I, II, and III of

the recombinant FSH with Organon and Serono, and Phase I, II, and III with recombinant LH of Serono, and I worked with Howard Jacobs in the early nineties, and we were the first to inject recombinant FSH to a patient with hypogonadotropic hypogonadism.

I remember that we stayed the whole night looking if there will be any reaction to this one small injection of recombinant FSH.

But since then we were stimulated to look at this unique disorder and we published our first paper in 1993, after extensive research in this group of patients. If we look at that old paper before the area of the recombinant FSH and LH, we can see that in order to get the patients pregnant, it is not the follicle, it's not the LH, the FSH, it's the combination.

We need to create an endocrine environment which will get the patient pregnant, and if we look at that old paper, we can always overcome with a lecker [ph] of LH with FSH. In 10 patients who were treated just with FSH, and at that time it was Metrodene, we received ovulation in three patients. The progesterone was high, but we felt in order to get them pregnant, because the endometrium was too

thick, although the estrogen was at some lower level.

So, it is not the follicle, it's not the progesterone, and it's not ovulation, it's to create the environment to get the patient pregnant which I think is the most important. FSH and LH are two gonadotropins that interact with each other. They are playing, they are talking with each other. It's not atroxin and paracetamol, it's two gonadotropins that influence the development of the follicles in the ovary.

Therefore, I think it is very important to get these two hormones in combination, to think about these two hormones as one.

If we look at that old paper, looking at the dose, what would be the appropriate dose, and this was before the study which was done with Serono. We can just easily calculate and find that the optimal LH dose in this group of patients is 100 IU.

We started with all our patients with 75, but we always had to increase the dose. You can always overcome the low LH dose with high FSH, but then you pay the consequences with these.

If you want to create a safe pregnancy,

then, you have to titrate the different gonadotropins in order to get the optimal results, and I think that 25 units of LH in order to start treatment is too low, 75 might be optimal although if you ask me how much I start with, I start with 75 and gradually increase the dose, but i never start with less than 75 units because I think it's a waste of time and it's waste of the drug, and the patients are paying for the drug, which is quite important.

I also want to comment about the definition of hypogonadotropic hypogonadism. Hypogonadotropic hypogonadism is the clinical syndrome, it's not a laboratory syndrome, we are not looking for LH and FSH.

We are looking for long-standing amenorrhea, low estrogen, thin endometrium with a combination of low LH and FSH in order to define this group of patients, for example, for ovarian failure, for menopause patients, but it's not the LH and the FSH which make the whole story, it's the low estrogen.

I was listening very carefully to the presentation of Dr. Liu, who presented hypothalamic amenorrhea, and it showed that you can have

hypogonadotropic amenorrhea even if you have high estrogen, and he showed that the estrogen might be approximately 140 pmol/L, which I think is high.

I think that there is no need in order to establish the definition for the progesterone challenge test because if you know how to do the ultrasound and how to scan the patients, if you have thin endometrium, you don't have to look to estrogen, you don't have to give the patient progesterone, they will not bleed.

In the paper we published long ago, 10 years ago, we showed that the mean level of estrogen was 43 pmol/L. If the estrogen level is less than 73 pmol/L, the patients will not bleed. If the endometrium level is thinner than 4 mm, you give progesterone as much as you want, the patient will not bleed.

So, it can be supported by the level of LH and FSH. It is very fine to have, it's very nice to have low level of LH and FSH, but in the paper, actually, we get to the counterpoint that the level of LH was 1.2. But if I have the patients with the same criteria with LH level of 2, for me they are hypogonadotropic hypogonadism.

The last thing I want to comment to is

about endpoint, which I had a discussion this morning. I don't think that we, as a physician, should reach an endpoint of pregnancy. It is very nice to have an endpoint of pregnancy, but our role as a physician and clinician is to restore physiology.

We have to restore normal physiology in these patients, and they will become pregnant, and if our endpoint is pregnancy, and we try to overcome the physiology, then, come the consequences. Then, we stimulate patients with too many follicles, we replace too many embryos because we want them to become pregnant, which is wrong.

I think that we have to restore physiology and the rest will be fine.

Thank you.

DR. GIUDICE: Thank you for your comments, as well.

Presentation of Questions and Committee Discussion

DR. GIUDICE: We now have six questions before the committee, and Dr. Slaughter had reviewed them. Perhaps we can also have them put up on the screen.

I would like to advise the committee that we need a vote on the first five questions. The

procedure for the vote is that the members of the committee--and we will start over here and go around, or start over here and go around--my understanding is that the members of the FDA who are sitting at the table do not vote. Is that correct? Okay.

The first question is--and this is actually falling right on the heels of what you have just heard from Dr. Shoham--Can subpopulations of hypogonadotropic hypogonadal women be identified solely by serum hormone, LH, FSH, E2 levels?

If you do not agree, what additional markers should be attained? Demonstration of withdrawal bleeding upon progestin challenge, DNA markers, Others.

If you do agree, were the appropriate subpopulations studied in Study 6905, 6253, and 21008?

Dr. Toner.

DR. TONER: I think the appropriate subpopulations were studied. The criteria used in those studies were not only these three endocrine markers, but also the amenorrhea that Dr. Shoham mentioned as an important sign. So, that would be my answer.

DR. GIUDICE: Dr. Dickey.

DR. DICKEY: I think I agree with Dr. Toner that they were. The question comes back perhaps though to the question raised in Dr. Slaughter's remarks, and that is, whether the robustness of the numbers in subpopulations were studied in that for some of the subgroups, there were very small populations, and I am somewhat concerned, keeping in mind the legal obligations I guess of the FDA.

DR. GIUDICE: I think we will get to that as we go down to other questions.

The first question is whether subpopulations can be identified by serum markers or other means. Dr. Liu presented some data this morning. Perhaps you would like to comment.

DR. LIU: The LH/FSH levels, when they are extremely low, the pulsatile activity is also concomitantly low, so there is less error in judging a subpopulation with extremely low gonadotropin levels.

So, in someone with HH, as opposed to a lesser severe disorder like the exercise-associated amenorrheas, it would be much easier to distinguish that population.

The estradiol levels, I think are fairly accurate if one does not use the rapid assay for estradiol, but a much more sensitive radioimmunoassay. A lot of the immunolyte assays that were used for IVF are totally inappropriate for determination of estradiol levels in this category where you are looking at between 40, 30, or 20 pg/ml, so a more sensitive RIA probably would be appropriate in establishing that.

Progestin challenge tests, we talked about it recently in an ACOG meeting of a variety of REs, and our feeling is that this is a bioassay for integrated estradiol exposure, but it does not really tell us the particular situation at that point in time when we assess the patient.

So, it is more of an integrated measure of estradiol activity, but clinicians still use it. Our feeling is it is probably not useful because if the patient spots, what does that mean versus having a full bleed, what does that mean, so there is a variation in response other than amenorrhea with respect to progestin challenge.

So, my feeling is it is not as reliable a tool as the biochemical measures we have.

DR. GIUDICE: Thank you.

Dr. Hager.

DR. HAGER: I would agree. I think that the objective evaluation of progestin challenge would leave it as a deficient method to evaluate, and I think that we are left, as has already been said, with the markers that were looked at, being LH, FSH, and estradiol.

I think as more specific assays become available, then, that is certainly the direction to go, but I would agree, I think that the subpopulations were identified in the only way that we could identify them, which was with these particular assays.

DR. GIUDICE: Dr. Stanford.

DR. STANFORD: I would agree except that I would point out that 6905 had different cutoffs, and am not comfortable that that particular study had the appropriate population.

DR. GIUDICE: I think also from Dr. Layman's discussion this morning, that we should all probably tuck in the back of our minds that within the near future, there likely will be genetic tests that will more clearly define different subpopulations that currently are not commercially available and certainly not in large

numbers.

So, the question is now--and I would like to go around the room unless there is any further discussion on No. 1--

DR. HAGER: I do have one question and that is, is the FDA asking for specific cutoffs, or is this a generalized question, are you asking for less than or equal 1.2 for LH, or is that the purpose?

DR. SLAUGHTER: The purpose was to have a consensus whether or not the subpopulations could be identified appropriately to put in a label by these markers as the population requiring treatment.

DR. GIUDICE: So, Dr. Slaughter, can you answer the question, do you want a cutoff?

DR. SLAUGHTER: If you agree that the markers were appropriate, yes.

DR. GIUDICE: Well, then, the question is different as stated here, because the question asks us can you distinguish subpopulations of hypogonadotropic hypogonadal women by the markers of LH, FSH, E2, unless you want to restate the question and ask us--let's answer that question first.

We will start on this side of the table for a change.

Dr. Rice.

DR. RICE: Yes.

DR. GIUDICE: Dr. Toner.

DR. TONER: Yes.

DR. BRZYSKI: Yes.

DR. STANFORD: Yes.

DR. EMMI: Yes.

DR. EMERSON: Yes.

DR. LIPSHULTZ: Yes.

DR. LIU: Yes.

DR. KEEFE: Yes.

DR. GIUDICE: Yes.

DR. DICKEY: Yes.

DR. TULMAN: Yes.

DR. LEWIS: Yes.

DR. MACONES: Yes.

DR. CROCKETT: Yes.

DR. HAGER: Yes.

DR. GIUDICE: Thank you. That is now unanimous. This is quite amazing.

So, then, the 1(a), if you will, we do not need to answer because we apparently all agree.

The second part of that question is, if

you do agree, were the appropriate subpopulations studied--and let's take it study by study--Study 6905? Let's go around the room, Valerie, starting with you.

DR. RICE: There were five people that met the criteria, so, yes, for those five, yes.

DR. GIUDICE: It's a subpopulation.

DR. RICE: Subpopulation of that study? So, the LH less than 1.2 group? What do you mean? A subpopulation of the population, of hypo/hypo.

DR. GIUDICE: Dr. Emerson.

DR. EMERSON: One of the issues would be that if you were to regard this study and trying to use the ideal or randomized, but then disregard part of the randomized therapy, that is somewhat problematic statistically, so I would interpret the question as do you believe the whole study is appropriate or not.

[All voted no.]

DR. GIUDICE: Next one is 6253. This is for the severely deficient, LH deficient, less than 1.2.

[All voted yes.]

DR. GIUDICE: Finally, 21008.

[All voted yes.]

DR. GIUDICE: I am almost afraid to ask the question. Since we have not truly been asked for a cutoff, we could go through the rest, and that may surface.

Let's go to No. 2. Was a placebo-controlled trial the appropriate trial design to demonstrate efficacy? If you disagree, should an active comparator trial have been considered?

Let's start on this side of the table now, Dr. Hager.

DR. HAGER: Are we discussing or yes or no here?

DR. GIUDICE: Yes, let's discuss this. I assume this is 21008 that you are referring to. Okay. So, this is the Phase III trial.

DR. HAGER: I think we have already discussed that for the initial trial, that the use of a placebo is the ideal way to go in a randomized, blinded trial.

I personally believe that as the data accumulate, that a comparator trial certainly has to be considered, so that colors my view on that. The initial trial, as stated, as a placebo-controlled trial, I believe is adequate. I

do believe there is need for a comparator trial.

DR. GIUDICE: Other discussion on this? Dr. Keefe.

DR. KEEFE: Since there is no FDA-approved treatment for the condition, I think the placebo-controlled was the only viable one at this point.

DR. GIUDICE: Anyone else want to make a comment? Dr. Crockett.

DR. CROCKETT: For the sake of future studies that may come up, when we may have an FDA-approved drug for this indication, I think the placebo is a standard that we should try to meet, but as we discussed yesterday, when we are taking care of this population of infertile patients, it can be difficult to always provide studies with a placebo.

I like the idea of having an active comparator or the crossover study that we discussed at length yesterday, and I think those should be viable options for this type of study.

DR. GIUDICE: Thank you.

DR. LIU: I really think the FDA ought to make some guidelines if you are going to do a placebo followed by a crossover, so that the drug

companies will know what standards they have to meet, and I don't think that is clear.

DR. GIUDICE: Thank you. Any other comments before we vote on No. 2?

Okay, we are going to start on this side of this table then. Dr. Hager.

[All voted yes.]

DR. GIUDICE: Once again unanimous.

The third question is: Should multiple cycles be considered for evaluation? Is there a priming effect of the first treatment cycle?

Dr. Slaughter, is the question under No. 3, is that an explanation of what the question is?

DR. SLAUGHTER: That's one of the explanations. Do you feel that exposure to the recombinant in the first cycle affected the subsequent cycles, and even to a gonadotropin at all in the first cycle affected subsequent cycles, and should we be using only the single cycle or multiple cycles?

DR. GIUDICE: Dr. Liu.

DR. LIU: Based on our observations with the GnRH patients, in general, the responsiveness in the second cycle on a variety of target tissues from the estrogen production from the first cycle

does affect your second cycle response.

This includes an increase in the size of the uterus gradually with estrogen priming and also the pituitary and/or cohort of follicles may be affected by the higher estrogen levels that are generated from the first cycle assuming the first cycle is not a placebo cycle.

So, there are really a variety of effects from the first cycle priming, and it may be difficult to independently analyze the first from subsequent cycles.

DR. GIUDICE: Dr. Keefe.

DR. KEEFE: It seems like a condition where there is only a few thousand people worldwide that are affected by it, and it has taken 10 years to recruit, should try to get any cycles they can.

Maybe Dr. Emerson could discuss how one evaluates cycles when there are two cycles from one person as opposed to two cycles from two people in terms of the data analysis.

DR. EMERSON: Well, as I talked about yesterday, the way I would do it, by did they get pregnant or not, or did they have whatever endpoint they were having. Again, the pregnancy would be my top choice, and it's a question of treating them on

those cycles post-randomization, and whatever happens happens, particularly in a blinded study, there should be no problem.

DR. EMMI: I guess my question is to Dr. Liu. Does a washout period between cycles make a difference in these cases?

DR. LIU: Biologically, if you were to suggest that there was some priming effect, it may affect the response in a subsequent cycle depending on the washout period, but no one has any data to suggest how much priming would occur or the length of the washout.

DR. GIUDICE: Dr. Emerson.

DR. EMERSON: In addition to the problems with the washout, and having to figure that out, which would prolong the study in terms of doing that, there is also issues related to the evidence that we heard suggesting that there should be some ability to titrate doses, and so on, so again, it's randomizing them to a strategy and allowing the clinicians to go forward in the most natural clinical manner would provide the greatest ability to discriminate between ineffective and effective treatments.

DR. GIUDICE: Dr. Toner.

DR. TONER: I would say that if the question really is do you have to look at multiple cycles to answer the question, I would say no, I think a single cycle, as a strategy for experimental design, ought to be sufficient in this situation. In fact, the later cycles may, because of priming and what you learn the first time, be even more successful, it amplified the difference, but a single cycle ought to be good enough.

DR. GIUDICE: Dr. Lewis, you had a comment?

DR. LEWIS: I was going to make the same point.

DR. GIUDICE: Okay. So, let me repeat the question. Should multiple cycles be considered for evaluation? It's a little vague, I think still, this question. Perhaps Dr. Slaughter or Dr. Shames could clarify this. Is this for study design?

DR. SLAUGHTER: I am sorry.

DR. GIUDICE: We are still a little confused about No. 3. Should multiple cycles be considered for evaluation? Is this for conducting a study for approval?

DR. SLAUGHTER: Yes, should we look at more than one cycle.

DR. GIUDICE: So, should the sponsor have built into the trial design more than one cycle?

DR. SLAUGHTER: Right.

DR. GIUDICE: As a requirement.

DR. SLAUGHTER: Yes.

DR. GIUDICE: Dr. Brzyski.

DR. BRZYSKI: I guess I am still trying to clarify the question. Are the options either FDA will never look at more than one cycle, or you always must have more than one cycle? Are those the two options?

DR. SLAUGHTER: This addresses just this trial or just should we have looked at more than one cycle for this trial for this indication.

DR. GIUDICE: This is specific to this?

DR. SLAUGHTER: Yes, today, it's specific Luveris.

DR. EMERSON: A question. But by that, do you mean that as this data is submitted now, that that would be the best analysis, or should the trial have originally been designed and with that specified as an endpoint?

Can I suggest that in the interest of expediency, so that you can use it, that we divide this into two questions? One is, is it

permissible, and the second is, is it preferable?

DR. SLAUGHTER: That's fine.

DR. GIUDICE: Perhaps someone can restate the question.

DR. DICKEY: Let me ask a question first and see if that helps.

DR. GIUDICE: Yes.

DR. DICKEY: If I recall the data, the only multiple cycles we looked at here were where patients were folded into the ongoing study.

Is your question here whether the data from those people who had been folded into a non-randomized study should be considered or not?

DR. SLAUGHTER: No, the question is really whether or not we should have looked at multiple cycles for trials for this indication. It's a design.

DR. GIUDICE: Dr. Toner.

DR. TONER: I think the first question is should multiple cycles have been required, so we can go around and answer that.

DR. GIUDICE: Dr. Rice and then we will go around.

DR. RICE: If I understand it. Should multiple cycles have been required for this study?

DR. GIUDICE: Correct.
DR. RICE: No.
DR. TONER: No.
DR. GIUDICE: Dr. Brzyski.
DR. BRZYSKI: No.
DR. STANFORD: I am going to say yes because I think that it would be better to have a pregnancy outcome, and then in that case, you would have to have multiple cycles to make it meaningful, but it would depend on your outcome that you choose.
DR. EMMI: No.
DR. EMERSON: I will put in a different disclaimer, but it is the idea of you would have to have a much larger sample size to please me, but, no, it doesn't have to be required.
DR. LIU: No.
DR. KEEFE: No.
DR. GIUDICE: No.
DR. DICKEY: No.
DR. TULMAN: No.
DR. LEWIS: No.
DR. MACONES: No.
DR. CROCKETT: No.
DR. HAGER: No.

DR. GIUDICE: Okay. Now, 3(b).

DR. EMERSON: Can we answer the question of whether we think it would be preferable, because the requirement is a very different issue to me.

DR. GIUDICE: It's Dr. Slaughter's question.

DR. SLAUGHTER: In looking forward to future designs, yes.

DR. GIUDICE: As preferable or required?

DR. SLAUGHTER: Required. No, we have already answered required, I think, and his question is can we get a vote on preferable. I think we can discuss that.

DR. GIUDICE: There is a comment here.

MS. JAIN: I just want to make it clear as to what we are voting on because there have been several reiterations of this question. I think what the committee voted on, unless I am confused, is whether there should have been multiple cycles required for this particular study, for this NDA. It did not address whether multiple cycles should have been required for a general study design.

If you want to have an answer to that question, then, we need to have a separate vote.

DR. SLAUGHTER: That's what they voted on,

I believe.

DR. GIUDICE: So, the next question is whether it is preferable in subsequent application.

DR. SLAUGHTER: I am not asking for a vote on that. I mean I think that you wanted to have a discussion on that.

DR. EMERSON: My point is, is I think it is preferable to use the multiple cycles, but again I agree that this question could be answered with a single cycle, it would just take a larger sample size to use a good endpoint, whereas, if you use multiple cycles, it doesn't take as large a sample size.

DR. GIUDICE: So, for the record, I guess the comment has been made that it would be preferable.

Shall we go on? Okay.

No. 4. Was it appropriate to use a surrogate endpoint for pregnancy, for example, follicular development in this study of hypogonadotropic hypogonadal women seeking pregnancy? We have already begun this discussion.

DR. HAGER: I would have a comment.

DR. GIUDICE: Yes, Dr. Hager.

DR. HAGER: It seems to me that it was

fairly clear to the sponsor from the FDA that ovulation was going to be the endpoint, and the sponsor chose to use follicular development, and I realize they have every right to do that, but it just seems to me that they would have taken that advice and for all the reasons that we have talked about pro and con.

We have talked about this over and over. I think that the endpoint, contrary to what was said just a moment ago, is clinical pregnancy. If I was going to drop back to another surrogate endpoint, I would at least desire ovulation rather than just follicular development.

DR. GIUDICE: I think it's important to remember that in looking at the pharmacologic action of the drug, that the endpoint obviously is going to be steroidogenesis and estradiol synthesis.

Many women in ovulation induction cycles, whether it is for a hypothalamic amenorrhea or other conditions, who have ovulation induction, there is not 100 percent correlation between follicle development, ovulation, and pregnancy.

So, in looking at the endpoint, when I read the data, and again I realize we all may have

different perspectives on this, but I want to know also, as a clinician, whether or not there is follicle development. My patient may not get pregnant, but she at least will have had follicle development.

Along with that follicle development is the issue of her estradiol level. So, when I look at the composite endpoint of the follicle size, which is primarily an FSH action, the circulating estradiol level, which is primarily an LH on the precursor synthesis, and a mid-luteal progesterone, to me, those are very powerful signs of a medication working or not working.

So, the question here--and I realize we are probably going to go round and round and round, and we could do this all night, but the question at hand is whether pregnancy--was it appropriate to use a surrogate endpoint for pregnancy, and the example given here is follicular development. It could have been ovulation induction in the study of hypo/hypo patients.

Dr. Rice.

DR. RICE: Where did we come up with this phrase "surrogate endpoint for pregnancy?" Was that in the NDA and I missed it or something?

Okay. So, why are even using surrogate endpoint for pregnancy, why aren't we just saying either follicular development or ovulation induction, because I think you sort of started to confuse things when you say surrogate endpoint for pregnancy.

Really, we are talking about follicular development and/or--it depends on whose version you want--ovulation induction. And I agree with you, in this population of patients, I am comfortable for many reasons that I think some of the people in the open forum really shared with us, that for many of these patients, to get to the point where they have follicular development, have a menses, is a success for them, and that to use pregnancy as an endpoint does not I think encompass the essence of what is happening to that patient.

So, I kind of view this patient as that very severe patient who is anovulatory, and if I get that patient to ovulate, which is expressed by follicular development and estradiol secretion, an increase in estradiol, then, I would feel like I have jumped a large hurdle in increasing her chances of getting pregnant or given her the opportunity to get pregnant.

When we talked about the group of patients who may not need pregnancy as that endpoint, it may be something earlier that we should have used as an endpoint, like follicular development, ovulation induction. I think this patient population fits that.

DR. GIUDICE: Dr. Lipshultz.

DR. LIPSHULTZ: Didn't we already decide on this yesterday?

DR. GIUDICE: Yes, we did.

DR. LIPSHULTZ: This was WHO-I that we said we would accept follicular development.

DR. GIUDICE: Correct.

Dr. Crockett.

DR. CROCKETT: I want to discuss a little bit more about what the criteria were used to determine follicular development. When we look at the recommendations from the FDA, going back to the Phase III trial, they recommended a much higher estradiol level, in fact, a cutoff of 200 pg/ml rather than the 109 pg/ml.

That is significant, and that makes that borderline 106 picogram patient much less on the borderline, so I would like some comment from the reproductive specialists on the board about which

would have been an appropriate measure of follicular success as far as an estradiol level.

DR. GIUDICE: Dr. Lewis.

DR. LEWIS: I wonder where 200 came from. That sounds high to me for this population of patients if they don't have a lot of follicles and they don't have much LH action.

DR. GIUDICE: Dr. Keefe.

DR. KEEFE: If a woman starts with a peak estradiol or a baseline estradiol of 40, and then goes up to 100-plus, they are going to ovulate. You are doing something significant.

I don't think we are ever going to see ovulation per se. That's a microscopic event, we are never going to see. We are always going to use a marker for that, and that is what we are discussing. I would say a rise from 40 to 100, 106, that's ovulation about to happen. It's as close as we can get to it.

DR. GIUDICE: Thank you.

DR. LIU: I would disagree that 100 is an appropriate marker. I think you are going to find the majority, in the normal menstrual cycle, it's about 300 to 350 picograms at the time of the LH surge, and that has been well established by very

sensitive RIAs, and it is repeatable.

With gonadotropins, you have an artificial environment and generally the estradiol production per follicle with gonadotropins are going to be lower, but 100 is still on the very low side, I think, and if you look at the endometrial development, that is inadequate for endometrial development unless you have an integrated maintenance of that 100 picograms for a long enough period of time.

So, in that particular patient that miscarried, I don't remember the endometrial thickness, but it certainly, probably was borderline.

DR. GIUDICE: Dr. Emerson.

DR. EMERSON: I have heard a lot of contradictions here today from the sponsor and from the various experts that simultaneously say this is a group that is just not going to get pregnant by themselves, where they need to have this luteinizing hormone therapy, and then the statement that was made by the sponsor was people are so happy when I tell them that they will have normal fertility.

If that is true, then, there is no problem

in using a good clinical endpoint in this trial, either that LH therapy will return them to normal fertility in which case it can be managed, or there is some question that it really works. So, in that case, we ought to see whether it works.

I would argue that a properly designed trial with this sample size or slightly larger would have stood a good chance based on anecdotal data that we have here, that I think we can only treat as observational data at this point, but it is suggestive that the effect might be in the range that another trial of approximately this size would work, and then why go to the surrogate endpoint.

DR. GIUDICE: Well, there are things in biology that we still don't understand in terms of implantation especially in women during the process of an ovulation induction cycle.

DR. EMERSON: I agree absolutely, so if we don't understand that biology, there is just the possibility that this therapy might actually be making it worse. So, again, if we don't know, then, we should answer it, given unlimited resources and unlimited numbers of patients, I would say answer those questions separately.

Let's answer the question at every single

stage, what can we do to increase follicle generation, what can we do to then have ovulation, what can we then do to have fertilization, what can we then do to have implantation, and go on to a live birth, that has no birth defects.

If you have unlimited resources, answer each one of those questions separately, but we don't have unlimited resources, it is attainable within this population to answer the bottom line question, which is the one that I think is ethical to answer both from the standpoint of the patients who suffer from infertility, I think that they would be very, very irritated if they found out 20 years from now that they had been spending an extra $10,000 for something that did not help them at all, or possibly was even harmful.

So, when we can answer the bottom line question, and we can never answer the mechanistic question in terms of ethics and efficiency, then, go ahead and make certain that we at least answer the bottom line question.

DR. GIUDICE: Well, we have heard the entire gamut from follicle development all the way through pregnancy. Yesterday, as a committee, we gave you our advice for this class of patients,

WHO-I, that we would recommend follicle development as the endpoint.

DR. EMERSON: I will just note there was not a vote on that, there was a consensus, but you can tell which way I would have voted.

DR. EMMI: I thought that what we decided was that pregnancy wasn't an appropriate clinical endpoint and that some other endpoint would be established, but I don't remember that we actually ever said whether it would be follicle development or ovulation.

DR. GIUDICE: Well, this is very germane to the question that is being asked because we, as a committee, need to make a decision (a) whether we think pregnancy should be an endpoint for now WHO-I patients, and, if not, then what the endpoint should be.

I mean do you want that information from us?

DR. SLAUGHTER: Pregnancy or live birth, and if you agree that a surrogate endpoint--I am sorry for using surrogate, but to me, surrogate is the endpoint you use when you can't measure the direct effect, so I am calling it surrogate--if you agree that a surrogate should have been used, what

surrogate should we have used.

DR. GIUDICE: Dr. Stanford.

DR. STANFORD: Two quick comments. My understanding of yesterday's discussion was we said that live pregnancy was the best, clinical pregnancy would be acceptable. In the case of WHO-I, if we could not attain that because of power, if we could not attain it for power, then, we would accept follicular development or I actually don't remember exactly what surrogate we said we would accept.

The question here seems to be a little bit one of fairness, because the FDA did tell the sponsor it would accept a surrogate, only the sponsor chose a different surrogate than what the FDA recommended.

So, we have a subquestion. But to me there is a fairness issue and that the FDA did indicate a willingness to accept a surrogate, and that is a little bit of an issue there.

DR. GIUDICE: Dr. Emerson.

DR. EMERSON: I note that, of course, everyone on the committee can vote their conscience, I vote my opinion, and the question, you know, the FDA is possible of doing things that

I don't think is appropriate, and I still give that opinion, so that is the question that I would answer is how should this trial be done that is credible evidence, not did they agree with the FDA.

Am I correct that this question is not did the sponsor agree with what you said?

DR. SLAUGHTER: Yes. It is simply your advice on which surrogate endpoint we should use, keeping in mind if there were to be future studies.

DR. GIUDICE: Then, do you want us to vote on the various endpoints?

DR. SLAUGHTER: No, this could be a discussion.

DR. GIUDICE: Dr. Hager.

DR. HAGER: May I read what we said yesterday? Drug manufacturers conducting studies for female infertility currently obtain the following indications: (a) induction of ovulation and pregnancy; (b) multiple follicular development and ART. These indications should be induction of ovulation and pregnancy, and multiple follicular development and ART and pregnancy.

So, we added "and pregnancy" to those yesterday.

DR. SLAUGHTER: Let me clarify how I

understand this. Yesterday, you said that you thought, in general, clinical pregnancy defined by presence of a fetal heartbeat to be used, in general, for ovulation induction, and ART to be exclusive of patients with WHO Type I.

Today, you said you thought that a surrogate would be possible, and you have now confirmed that we shouldn't look at pregnancy, we shouldn't be trying to establish a difference in pregnancy.

If we don't do that, what should we look at?

DR. GIUDICE: And the options that we have discussed so far are follicle development or ovulation induction.

DR. SLAUGHTER: Follicle development defined on ultrasound, ultrasound plus hormone levels, how?

DR. GIUDICE: We can discuss that.

Dr. Stanford.

DR. STANFORD: I think follicular development, if it's accepted as an endpoint. I think ovulation is probably better, but if follicular development is accepted as an endpoint, I don't think cancellation of cycles due to risk of

OHSS should be included as follicular development.

DR. RICE: Are we having a general discussion or are we discussing this product and this study? I think we are getting off track here. We have to give a decision on this product today, so we need to--I mean it is already defined. They defined follicular development, you gave some criteria, you had some definitions for ovulation induction.

So, we have to decide on whether or not the sponsor met the criteria that was laid out to them, whether follicular development or ovulation induction. I mean there may be subsequent some additional time when we can beat this idea again in the ground, but I think we need to decide on this product, and we are getting away from that.

DR. GIUDICE: Is our charge to decide whether or not the sponsor complied with the recommendations of the FDA, or whether the endpoints that were used were appropriate for the study?

DR. SLAUGHTER: The latter.

DR. GIUDICE: Thank you.

Dr. Brzyski and then Dr. Emerson.

DR. BRZYSKI: Let me go back to that

comment that you made specifically looking at this product and the pharmacologic effect. Somehow a consideration of estradiol production, I think needs to be considered or thought about because even in the sponsor's presentation, referring back to Dr. Shoham's experience, there are patients that will develop follicles measurable on ultrasound in the absence of estradiol production on pure FSH.

So, to show efficacy of the LH, which we have a pretty good idea how it works and what it does, somehow I think you need to get the estradiol into that calculation as a surrogate.

DR. GIUDICE: Dr. Emerson.

DR. EMERSON: I was just going to suggest three yes or no votes to try to address those three major points. Ask one question of whether the study should have evaluated clinical pregnancy. That seems to be sort of a dividing point. The next one would be ovulation defined by a mid-luteal progesterone level, and not counting a risk of OHSS as an endpoint. The third level is a yes or no question on follicular development.

DR. GIUDICE: Dr. Rice.

DR. RICE: That first question is not, in my opinion, appropriate for us to answer. The FDA

and the sponsor, the only thing they are disagreeing on is whether or not they should have taken out ovulation induction. They never had an endpoint of clinical pregnancy on the table.

Now, we can answer your question when we get down to 6. If we get down to 6 and you said there are additional studies that need to be done that address clinical pregnancy, we can have that discussion, but we shouldn't be voting today, in my opinion, to say whether or not they should have added clinical pregnancy to that, because that is not the question before us.

DR. EMERSON: We are a scientific advisory board that is not subject to the FDA, nor subject to the sponsor. They want our opinions. So, if we can just as easily say that we think the FDA messed up, or we think the sponsor messed up, and that is our role. Our role is to give our opinions.

DR. GIUDICE: I think this is not a boxing match, so I think we really need to hone in and focus in on the issues at hand.

What I have heard the FDA say is that you want our opinion about an appropriate surrogate or an appropriate endpoint, and the options are either follicle development defined by--and this is this

particular NDA that we are addressing--defined by follicle size, an estradiol level of greater than 109 or 106--109, and a progesterone level greater than 7.9 pg/ml.

That's not what your question says, but what we are addressing, as I understand it, is the appropriateness of the endpoints put forward by the sponsor.

DR. SLAUGHTER: Yes.

DR. GIUDICE: It is very difficult for us to come up with our questions.

DR. SLAUGHTER: Let me try this one more time. If you don't agree--and we have gotten past the clinical pregnancy thing--if you are saying in WHO Type I, you should look at something short of pregnancy, what is it?

DR. GIUDICE: Is this for general studies or for this particular study?

DR. SLAUGHTER: This is for general studies. I am not going to ask you to comment on the appropriateness of it for this study, because that is what was done.

DR. GIUDICE: So, then, we did that yesterday and we don't need to vote on that, do we, because it not specifically address--

DR. SLAUGHTER: Not for Group 1, I didn't understand you to have done that for Group 1.

DR. GIUDICE: Perhaps we can repeat this then. Would someone like to summarize what we decided yesterday? Dr. Hager read it. I think what Dr. Slaughter is asking for is the follicle size, am I right or not?

DR. SLAUGHTER: How would you define follicular development, should it be defined for all three of the criterion as the sponsor did here? If you are saying you should look at follicular development, should it be based on follicle size, estrogen, and progestin, or are you talking about just an appearance on ultrasound, follicles?

And one other thing. Is estradiol and progesterone sufficient, should we also be looking at other factors that might come in for follicular development? This is for future considerations.

DR. GIUDICE: Dr. Toner.

DR. TONER: I would say that in the context of this study, for this drug, it is not inappropriate at all to look for the follicles to grow, estrogen to be produced, and then progesterone to be above a certain level, but those criteria that here define follicle development

might not be the pertinent ones if another drug that also has a role in follicle growth was being considered.

So, again, for this particular product, I think these are satisfactory criteria to judge efficacy.

DR. GIUDICE: Dr. Crockett.

DR. CROCKETT: I was just going to make a suggestion that we kind of make a list of most preferable to least preferable evidence to consider for future drugs, and I would put forth that a pregnancy of any kind would be definite evidence of ovulation, that the progesterone levels and the estrogen and FSH and LH levels that we have discussed may be considered in some cases as acceptable evidence or probable ovulation, but I would want to use Dr. Liu's numbers rather than the lower numbers that were suggested in this study.

I would suggest that folliculogenesis or growth by ultrasound or other means, by itself, should not be considered evidence of ovulation because so much of the background information that we heard, that other things, you know, the LH and the quality of the egg are important in determining whether ovulation occurs or not.

For that reason, I would also not include the OHSS patients as proof of ovulation.

DR. GIUDICE: Okay. I would like to address the OHSS patients because that does get to the last bullet on that question. To have an outcome or to look at that, of OHSS as an endpoint, is a bit peculiar, and I think when we all have read these data, I don't quite think that that's going to be one of the issues in terms of showing efficacy of drug.

However, you are never going to get OHSS unless you have follicle development, so I would still argue that for this particular NDA, that it was an appropriate choice. In general, however, and this is where I think the FDA perhaps can use our help, and that is, whether this should be considered as an endpoint of the proof of either follicle development or ovulation in the future.

Dr. Keefe and then Dr. Lewis.

DR. KEEFE: I agree. Imagine if were to go back 80 years and we are looking at a new drug called insulin, and somebody gets hypoglycemia, and we say oh, it doesn't count. You know, we are just looking to try to control hypoglycemia, but we are not going to count that because it is not

officially optimal control.

I mean you have got to start somewhere. We probably spent one year of somebody's time for each patient, each cycle that somebody is going to be taking this, and I think we are missing the point. We are restoring physiological function for a group of patients that have very few alternatives. We should keep that in the context.

DR. GIUDICE: Dr. Lewis.

DR. LEWIS: Well, I think it depends very largely on how you define OHSS and for what study. If you say that it was defined as patients who had a certain number of 15-millimeter follicles, which is a large follicle, plus a high estradiol, then, I agree that that indicates the drug worked, but we just heard that FSH action alone is sufficient to get a large number of follicles, and if you had a little bit of estrogen from a large number of small follicles, guess what. Your estrogen would go up.

So, I think you have to be very careful how you define OHSS, and as a general rule, it's not--you just have to be careful if you are going to use that as a means of saying that that is drug efficacy.

MS. WILLIAMSON JOYCE: Pardon me. I just

want to remind that we are not talking about OHSS, we are talking risk, and again, the very low, low cutoff that we put, which is not necessarily the criteria that you would necessarily use to cancel a cycle.

DR. LEWIS: Right. I am not arguing that that was appropriate, and I do think it did show that the drug had some effect.

DR. GIUDICE: Dr. Crockett.

DR. CROCKETT: I am not sure that it does show that the drug had some effect. We have seen and heard testimony that you can blast somebody with FSH and get follicular growth all by itself. In fact, we saw that in some of our placebo patients. There was one placebo that was removed from their study that had OHSS and didn't even have the LH challenge.

So, my point being again you can have follicular growth without LH, and if you are looking at a recombinant LH product, that in and of itself does not indicate that it worked.

DR. GIUDICE: Dr. Macones.

DR. MACONES: I would just add that as we think about this, we are not just thinking about approving a drug, we are thinking about approving a

drug at a dose, so the question of safety, I think is very relevant, whether the 75 units of recombinant LH is both effective and safe.

To me, that is where the OHSS question or the risk of OHSS comes in is whether or not this is the right dose for this drug.

DR. SLAUGHTER: Actually, a consideration for the patients who were taken out of the study and the cycles canceled, whether you really considered that as evidence that the drug is working, and in the end, that we should approve or we should consider that that drug showed efficacy for the endpoint.

MS. WILLIAMSON JOYCE: Again, just for the sake of accuracy, the patients were not removed from the study. There were no patients whose--the cycle cancellations did not remove the patients from the study.

DR. SLAUGHTER: All right. Let me rephrase that. Patients whose cycles were canceled for risk of OHSS, does that show efficacy?

DR. GIUDICE: Dr. Toner.

DR. TONER: It does for me. Under the condition that apart from follicle growth, which probably didn't have anything to do with the LH,

they went on to have estrogen production and progesterone production, which we have been assured has happened in those who were dropped from the study at that point. So, I would take that as efficacy of the drug doing what we hope the drug will do.

DR. GIUDICE: Dr. Emerson.

DR. EMERSON: To introduce a slightly different analogy than the diabetes, in hepatorenal syndrome, people did try dialysis to see if that would not cure it, because the people apparently had kidney failure after severe liver failure. They did try it. If they had used your criterion that, oh, well, we modified the BUN, dialysis does modify the BUN, it does not change survival one iota, and we would be dialyzing an awful lot of moribund patients today.

The criterion is not just in a surrogate marker that is perfectly predictive in a natural state, once you intervene on that population, you cannot count on that same covariance, the same correlations which are your final endpoint, and there is a level of scientific credibility we need to say that that still obtains.

DR. GIUDICE: Dr. Rice.

DR. RICE: I have a note written down here, and I just want to clarify this. The question was asked earlier, in those patients at risk for OHSS, that those patients were canceled because of follicular development, and five of those patients had no appropriate increase in estradiol production. Is that incorrect? So, what is the correct answer?

MS. WILLIAMSON JOYCE: Yes, it is incorrect.

DR. RICE: So, what is the correct answer?

DR. KENLEY: Three were canceled because of large follicles. That is three follicles greater than 15 mm. One was on placebo and two were 75.

DR. RICE: Before you go to the next part, what were those patients' estradiol, was it appropriate, was it increased? Did they have concomitant--I know you have the results.

DR. KENLEY: They were greater than 109, and--

DR. RICE: No, no, go on. I want you to tell me about the rest of them.

DR. KENLEY: And four patients were canceled because they had large estradiol. Two of

those patients also had follicles.

DR. RICE: So, essentially, four of those patients out of seven--

MS. WILLIAMSON JOYCE: Out of six.

DR. RICE: Okay. Four out of six of them had appropriate increases in estradiol with follicular development.

DR. KENLEY: Yes.

DR. RICE: And estradiol, you are saying is appropriate, is greater than 109.

DR. KENLEY: Well, no, they were greater than 1,100, because they were canceled.

DR. RICE: But only four of those, but two of them, you haven't told me what the estradiol was. You just told me it was greater than 109.

DR. KENLEY: Do you want to know what the estradiols are?

DR. RICE: Yes.

DR. KENLEY: One was 423 and the other one was 556.

DR. RICE: So, they had increases in their estradiol.

DR. KENLEY: Yes.

DR. RICE: Now, let me ask this question. If you add those people into the analysis, in your

calculation, is your data statistically significant, is it significantly different?

DR. GIUDICE: Dr. Rice, what is your question?

DR. RICE: My question is, if you add those patients back in as successes, do we have statistical significance, or do we have a difference?

DR. GIUDICE: By the FDA analysis?

DR. RICE: By the FDA analysis. I am asking FDA, if they take those six patients--

DR. SLAUGHTER: Can you address that? If you add the four patients back who had--

DR. RICE: Six.

DR. SLAUGHTER: Is it six?

DR. RICE: It would have to be six because she said two of them had estradiol levels, one was 400 and something, one was 500 and something. Those two and then the other four had estradiols over 1,000.

DR. SLAUGHTER: If you don't count the ones who were canceled for OHSS as failures, then, yes, it would have been significant.

DR. RICE: Okay. So, adding those six back makes it significant.

DR. GIUDICE: Dr. Emmi.

DR. EMMI: I am a little confused. I agree that we could look at the data for the OHSS patients. What I am confused about is did they actually meet their criteria that was set forth. I understand we are not getting progesterones probably because they weren't drawn, but did they have the size of development that the study had said was necessary, and did they have the amount of estradiol per follicle that was necessary, and I am not clear on this.

DR. RICE: From my understanding, they had the size because of all of them had large size follicles.

DR. EMMI: Fifteen.

DR. RICE: Fifteen millimeters.

DR. EMMI: Fifteen, not 17, which I thought was the criteria.

DR. RICE: But 15 mm was the criteria for canceling for risk.

DR. EMMI: Right, and what I am asking is if you are going to say that they met criteria for including them in the folliculogenesis phase, then, I think they needed to meet the criteria that were laid out by the study, which is 17 mm, and if they

continued in the study, then, do they have that data? Do you understand what I am saying?

It's 15 versus 17, and if they had 20 follicles with the estradiol 500, or if they had 6 follicles with the estradiol 500, it makes a difference in the quality of folliculogenesis to me, and I don't have that data available is what I am saying.

DR. GIUDICE: Let me just try to bring us together here. I am not sure we have that information, but from what I have heard, it sounds like the estradiol levels were 4- and 500, and you don't usually get that from even 107-mm follicles. You need some kind of LH action.

We are supposed to adjourn at 5 o'clock, however, many of the flights to the West Coast actually stop leaving Washington at around 6:30, so we are going to lose some of our committee members in about half an hour.

Because the FDA wants us to--No. 4 has been converted to a discussion, and I hope that we have given you enough information regarding parameters.

The other number that we have been asked to vote on is No. 5, and that is: Are the data

sufficient to establish efficacy for ovulation induction? Then, we will get to No. 6. That will be in a discussion format.

Dr. Shames.

DR. SHAMES: I want to make things very clear when it comes to No. 5. Five is really the essential question. There is no doubt we have got to answer the question is the data sufficient to establish efficacy for ovulation induction.

The reason for that is because that is the indication that is in the NDA, which we did not approve.

Now, several weeks ago the sponsor did ask or request a re-analysis or discussion regarding follicular development. If the sponsor wants to do that, then, they need to resubmit data to us, and we can consider that as something called a complete response. That is another issue.

The issue is, though, we need to know the answer to No. 5 as it pertains to ovulation induction. If we discuss follicular development, I am not going to know what to do about that, because that is not the indication that was in the NDA.

So, we can have discussion about follicular development, but we need to know the

answer to Question 5 as it pertains to ovulation induction.

MS. WILLIAMSON JOYCE: I am sorry. Then, I would suggest that perhaps the question should include the--I mean we did include follicular development in the NDA indication.

DR. GIUDICE: Can the FDA give us some guidance here? The sponsor is stating that what they had was follicle development and ovulation induction, and then they dropped the ovulation induction for other reasons.

DR. RICE: Why can't we vote on them separately? Why can't we vote on them as follicular development, and then we can vote on ovulation induction, and then you all can decide if you have the right information.

DR. SLAUGHTER: Ovulation induction first, please.

DR. GIUDICE: Okay. Would you define that for us, please?

DR. SLAUGHTER: We base ovulation induction on the progesterone level alone.

DR. GIUDICE: Okay. Is there any discussion about this before we vote? Yes, Dr. Emerson.

DR. EMERSON: Also, it generally takes more than one study to really establish these things. It is not the idea that do they have one result, and what the FDA claimed, and which I personally concur with, is that the 6905 study, well, actually, we all concurred with that unanimously, that that was not too germane to this point, and that neither of these studies stand on their own when you do not count the OHSS as an endpoint, that neither of them achieve any level of statistical significance.

The Phase II study was an unblinded study, as well, so it is really there is this real paucity of scientific evidence and credibility that is lacking on this submission.

DR. GIUDICE: Dr. Rice.

DR. RICE: Is that data that we have for ovulation induction, as you define it, as progesterone, greater than 7.9? Is the correct data that we have from Slide 46 of your presentation? Because as I can recall, Serono, did you present any data to us on progesterone levels? If you did, maybe you want to put it up.

MS. WILLIAMSON JOYCE: Yes.

DR. RICE: Which slide is it?

MS. WILLIAMSON JOYCE: First of all, the p4 was one of the three elements of the composite endpoint. So, we have the composite endpoint plus any indication of pregnancy as being a success.

The study, however, was not prospectively defined using ovulation rates as the endpoint. So, we have data on p4, but any statistical analyses done post-hoc on a single element of that composite endpoint need to be considered for what they are.

DR. RICE: When you all agree, the pre-meeting that you had when you had the discussion, I mean what you were defining ovulation induction as? You didn't agree what you were going to define ovulation induction as?

MS. WILLIAMSON JOYCE: We have always defined the endpoint as the composite endpoint of follicular development with those three elements plus any sign of pregnancy, whether it be a positive beta hCG or confirmed by ultrasound.

Again, we agreed in the meeting of May of 1999 that the FDA recommended that we use ovulation rates as the endpoint measured by p4, and that recommendation was considered carefully along with all of the other recommendations including the blinding of the study, but we continued to maintain

that the composite endpoint of follicular development as defined prospectively in the protocol, and as also defined in 6253, was the correct endpoint.

DR. GIUDICE: Just before getting to Dr. Crockett, the composite endpoint, it is not one or two or three, it's all three of them, so it's the follicle size, the estradiol, and the progesterone, it's not just a single progesterone level. I just wanted to make that clear.

DR. SLAUGHTER: Along with the escape, the cycles are canceled.

DR. GIUDICE: Yes, and along with any pregnancy.

Dr. Crockett.

DR. CROCKETT: Just a point of clarification. In the large green folder that we were supplied with, there is a copy of amended NDA from 2001, Section 2.3 in our folder, and it clearly says that the indication at that time was stimulation of follicular development and ovulation in infertile women with LH and FSH deficiencies.

Am I mistaken?

DR. GIUDICE: Yes, I don't think that is the NDA. I think that was the penultimate one.

MS. JAIN: What the sponsor is referring to is an additional amendment that they sent in August of this year.

DR. CROCKETT: In August of 2003?

MS. JAIN: Yes.

DR. CROCKETT: This is the NDA from 2001.

MS. WILLIAMSON JOYCE: No, these are the medical reviewers and the statistical reviewers' reviews of the original NDA.

DR. CROCKETT: So, we don't have a copy of what the original NDA said or what the NDA from 2001 said as the indication?

DR. SLAUGHTER: No, I don't have that label with me.

DR. GIUDICE: Can we get back on track here.

Dr. Keefe.

DR. KEEFE: It seems to me most of the crux of the argument rests in Serono's or the sponsor's table at the bottom of page 29 of their presentation, and the FDA's at the bottom of page 14, and just lining up those two tables, there is one cell that differs, and that's in Luveris treatment, you know, the FDA claims there is 16 out of 26, and Serono claims it's 17 out of 26, so if

we could just find out about why those numbers differ. I mean that is the crux of it, right, that's where they really differ. That is where the rubber meets the road.

DR. GIUDICE: That was that one patient.

DR. KEEFE: That's the one patient. So, that is what we should be discussing, right? The pregnant patient.

DR. SLAUGHTER: I just wanted to get back. I don't have the label, but when I put up the screen, I copied that directly from the label.

I also have the medical officer's review that put the labels, applicant's proposed indication for concomitant administration with recombinant human follicle stimulation hormone for the induction of ovulation in infertile women with severe LH and FSH deficiency.

DR. GIUDICE: Thank you.

We are now trying to address the issue of whether or not the data are sufficient to establish efficacy for ovulation induction where ovulation induction has been defined by the FDA apparently as a p4, and by the sponsor as a composite endpoint including OHSS patients and also pregnancy defined from chemical through clinical.

Dr. Stanford.

DR. STANFORD: Again, can we vote on those separately? Let's vote first on the p4 definition and then, second, on the sponsor definition.

DR. GIUDICE: If the FDA wants us to do that. Do you want us to do that, or how do you want us to define ovulation induction? Then, we will go to follicular development.

DR. STANFORD: And if I am understanding what the sponsor is saying in making their revision of their indication, is they are actually not defining ovulation induction, they are actually defining follicular development, because they submitted a modification to their NDA to say what we want to approve is for follicular development, and that is their definition of follicular development.

DR. GIUDICE: Dr. Slaughter.

DR. SLAUGHTER: Yes. We would like you to take a vote on both. Take it on ovulation induction as defined by the sponsor's follicular development, looking at the data as proposed by the sponsor and the FDA, and ovulation induction as defined by progesterone level, looking at the data as put up by the FDA.

I don't think the sponsor gave you progesterone-only data.

DR. GIUDICE: I don't think we have that information.

MS. WILLIAMSON JOYCE: No, we wouldn't have done that. That was post hoc on an endpoint that wasn't--

DR. GIUDICE: Other discussion about this? Dr. Keefe.

DR. KEEFE: Just a question. The patient, the pivotal patient who got pregnant, did she have a progesterone level drawn?

DR. SLAUGHTER: Yes, she did, and she would have been counted as a positive in the progesterone analysis.

Kate, can you put up your progesterone analysis again.

DR. GIUDICE: Dr. Emerson and then Dr. Lammers.

DR. EMERSON: Just as a parting shot because I have to go, but I think if you listen to us very, very closely, as we are sitting and discussing one patient and saying how this one patient would sway us one way or the other, I don't think it takes being a statistician to say that

that is not exactly credible evidence.

I would hope that we would operate where one patient didn't make a difference.

DR. GIUDICE: Dr. Lammers.

DR. LAMMERS: Can I have the slide on, please.

DR. SLAUGHTER: Excuse me. Can we go ahead and proceed to the vote? People are leaving, and we would like to take the full benefit of people being here, so can we please vote?

DR. LAMMERS: Can I reply to Dr. Keefe's question briefly? She had a p4 value of 13.2 nanograms per ml.

DR. GIUDICE: So, you want us to vote. Let's first vote on whether or not the data are sufficient to establish efficacy for ovulation induction (a) as defined by the sponsor.

So, that includes the three parameters that are and, not or, follicle development, estradiol, and progesterone, and also including the patients who were canceled for risk of ovarian hyperstimulation syndrome, and also patients who had pregnancy of any type.

So, we will start with Dr. Hager.

[Vote taken.]

DR. GIUDICE: Now, the second is to answer the question, the same question, but with the FDA definition of ovulation by a progesterone level. Understand that on both sides, there are issues, the whole issue of doing that analysis without having it prospectively put into the protocol.

[All voted no.]

DR. GIUDICE: The follicle development piece. Now, we are going to take a vote unless--no, there is no further discussion--on whether or not the--let's give it the same level of rigor--are the data sufficient to establish efficacy for follicle development, and the only definition of follicle development that we have is the sponsor's.

We will start on this side of the table.

[Vote taken.]

DR. GIUDICE: Any other subpieces of No. 5 that you want votes on? Okay.

We are just doing the tallies here. We have no hanging chads, so we have to be sure we have everybody.

Drs. Brzyski, Stanford, and Emmi, there was a lapse here of receiving your information, so could you please restate your vote for the last

one.

Brzyski said yes, Stanford no, Emmi yes.

We are now down to No. 6, and that is: If additional clinical studies are recommended, what type of study or studies should the Division request in order to provide sufficient evidence of efficacy? Should additional studies evaluate lower doses for efficacy?

This is now open for discussion, and we are not voting on this. Correct?

DR. SLAUGHTER: Correct.

DR. GIUDICE: Dr. Toner.

DR. TONER: My vote would be not to bother about lower doses. We use doses higher than this all the time clinically without any evidence of harm. I would rather invest the time and money in trying to free up the investigator for varying the FSH dose as they go to avoid the problem of OHSS cancellation risk.

DR. GIUDICE: Dr. Stanford.

DR. STANFORD: I agree with that. I fully agree with that, that if a future study is done, the ideal design would be double-blind with the 75 IU, with yes or no with the double-blind, and then the investigator is left free to vary the FSH dose,

and I would argue for an outcome of clinical pregnancy with multiple cycles.

DR. GIUDICE: I think it is going to be quite a challenge to find that many hypothalamic hypo/hypo patients, but it's the study design that we are after.

DR. STANFORD: I am just making my opinion, and I would refer again to what Dr. Emerson said, and again I would defer to him for power calculations, but he is of the opinion it wouldn't take that many more than what we have got.

DR. GIUDICE: Thank you.

Any other discussion? Additional studies to be proposed? Yes, Dr. Tulman.

DR. TULMAN: I would just like to propose that since we voted to approve this drug for a very limited population, although not to disparage this population in any way, but the evidence for the drug and our approval for it is based on a very limited population, and if this drug were to be approved and used, it would probably wind up being used in a larger population, and I don't think that we really have the evidence to say what would happen in that larger population. I think we need that research both for safety, as well as efficacy.

DR. GIUDICE: I just want to clarify that this committee has not done any approval of any drug.

DR. TULMAN: I believe I said were to be.

DR. GIUDICE: Were to be.

DR. TULMAN: Were to be.

DR. GIUDICE: Thank you.

Dr. Hager.

DR. HAGER: I would just echo that again. I think that our recommendations heard today are for a very narrow, specific population, and even a subpopulation of that group with very low LH levels, and to discourage the use in a general population.

You can just see where this could go with off-label use. I think that what you have heard today is that we don't see the evidence, barely evidence of effectiveness, and a sincere concern about extending this use to patients off label.

DR. GIUDICE: Dr. Rice.

DR. RICE: I think it has also been evident from our discussions that the communication between the FDA and the sponsors needs to become more transparent and clear, and that a lot of this confusion probably could have been avoided if there

was some better documentation.

I think it puts the committee in a difficult situation when we are not clear about what we are to provide advice on. So, I would hope that in the future, that there is some improved communication such that we can make sure that we can fulfill our duty, and that is to make our recommendations that is based on very good, sound evidence and a clear understanding of what the expectations were that the sponsor were to meet from the FDA.

DR. GIUDICE: I just want to clarify something that Dr. Hager said. I am not sure I heard this correctly or maybe I did, but I am not sure I agree with it, and that is that the FDA has heard from us a committee that there is not much information about efficacy.

Is that what you said? If you could clarify that, please.

DR. HAGER: What I was saying was that the FDA has heard our deliberations regarding the efficacy of this drug. I didn't say that it wasn't effective. I said they have heard our deliberations about the efficacy, but I have a concern also about off label.

DR. GIUDICE: Thank you.

I am wondering if the FDA could let us know, now that you have some information from us in an advisory capacity, what you will do with that and what the next step will be.

DR. SHAMES: Well, I will give you a bureaucratic answer. I guess the answer is that we will evaluate these various votes and evaluate the comments, and meet internally to see how we will move forward. I didn't even count up the votes, but you did.

I thought I heard that from the p4 definition, the data was not sufficient. Is that the vote?

DR. GIUDICE: The p4 was uniformly no.

DR. SHAMES: Right.

DR. GIUDICE: And the ovulation induction by the sponsor's definition, we have to determine what that is for the final tally. Apparently, that is going to come out in the minutes that Shalini will pass out just to the committee participants.

DR. SHAMES: We will go back and have our own internal discussions and come to some conclusion. As you know, we weigh heavily your opinion, and we have to exactly extract what that

was. Then, it is ultimately up to us to come to the decision.

Of course, we interact now with the sponsor to see what will come with this, ultimately, how we will go.

DR. GIUDICE: Thank you.

Is there anyone who wants to make any additional comments before we conclude?

MS. WILLIAMSON JOYCE: I would. First of all, I would like to thank the Division for bringing this NDA before an advisory committee. This is an important part of the process. I would like to thank all of you for having spent the two days here and stayed long enough to go through the entire process, and just to say on behalf of Serono we do look forward to continued discussions with the agency, so that we can bring this application to approval.

Thank you.

DR. GIUDICE: Shalini has a comment to make.

MS. JAIN: I just wanted to say thanks also to all the committee participants today, both our SG consultants and the committee members, as well as the division representatives, and wanted to

let people know that if they would like to leave their briefing documents, they can do so, and I will mail them back to your home or work if you would just specify what you would prefer.

Also, for those of you that need to catch your flights immediately, there are shuttle drivers outside the store that can take you to whichever airport you had designated to me previous to today.

Thanks.

DR. GIUDICE: I also would like to convey my thanks to the committee members and to all participants and to the sponsor for their contributions today.

Our meeting is now officially adjourned.

Thank you.

[Whereupon, at 4:00 p.m., the meeting was concluded.]

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