Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Advisory Committee for Reproductive Health Drugs
August 29, 2006
620 Perry Parkway, Gaithersburg, Maryland

Advisory Committee for Reproductive Health Drugs Members Present (Voting):
Arthur L. Burnett, II, M.D.
Diane Merritt, M.D.
James R. Scott, M.D.
William D. Steers, M.D.
Lorraine J. Tulman, DNSc, RN, FAAN
O. Lenaine Westney, M.D.

Advisory Committee for Reproductive Health Drugs Consultants (voting):
Maria Bustillo, M.D.
Sandra Carson, M.D.
Daniel Gillen, Ph.D.
Julia V. Johnson, M.D.
James Liu, M.D.
Elizabeth Shanklin-Selby (Patient Representative)
Ezra Davidson, M.D.
Karin B. Nelson, M.D.
Joseph Harris, M.D.
Cassandra Henderson, M.D.
Katharine Wenstrom, M.D.
Gary B. Hankins, M.D.
Hyagriv Simhan, M.D.
Vivian Lewis, M.D.
Rose Viscardi, M.D.

Industry Representative (non-voting):
Steven Ryder, M.D. – Acting Industry Representative

Advisory Committee for Reproductive Health Drugs Members Absent:
Charles Lockwood, M.D.
Ronald S. Gibbs, M.D.
Jonathan Tobert (Industry Representative)

FDA Participants:
Julie Beitz, M.D.
Dan Shames, M.D.
Scott Monroe, M.D.
Lisa Kammerman, Ph.D.
Barbara Wesley, M.D.

Open Public Hearing Speakers:
Barbara Dehn
Jackie Duda
Nancy Green
Terri Grossklaus
Joseph Hwang
Senator Connie Lawson (Indiana)
Michael Paidas
Davene White
Cynthia Pearson

Designated Federal Official
Teresa A. Watkins

I certify that I attended the August 29, 2006 meeting of the Advisory Committee for Reproductive Health Drugs and that these minutes accurately reflect what transpired.

_____/S/_____
Teresa A. Watkins
Designated Federal Official

_____/S/_____
Ezra Davidson, M.D.
Acting Chair, ACRHD

FINAL Minutes
Advisory Committee for Reproductive Health Drugs Meeting
August 29, 2006

A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at: http://www.fda.gov/ohrms/dockets/ac/cder06.html#rhdac

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

Prior to the meeting, the members and the invited consultants were provided the background material from the FDA. The meeting was called to order by Ezra Davidson, M.D. (Acting Chair, ACRHD); the conflict of interest statement was read into the record by Teresa Watkins (Designated Federal Official). There were approximately 175 persons in attendance. There were 9 speakers for the Open Public Hearing Session (see below for a listing of the speakers).

Attendance:
Advisory Committee for Reproductive Health Drugs Members Present (voting)
Arthur L. Burnett, II, M.D., Diane Merritt, M.D., James R. Scott, M.D., William D. Steers, M.D., Lorraine J. Tulman, DNSc, RN, FAAN, O. Lenaine Westney, M.D.

Advisory Committee for Reproductive Health Drugs Consultants (voting):
Maria Bustillo, M.D., Sandra Carson, M.D., Daniel Gillen, Ph.D., Julia V. Johnson, M.D., James Liu, M.D., Elizabeth Shanklin-Selby (Patient Representative), Ezra Davidson, M.D., Karin B. Nelson, M.D., Joseph Harris, M.D., Cassandra Henderson, M.D., Katharine Wenstrom, M.D., Gary B. Hankins, M.D., Hyagriv Simhan, M.D. Vivian Lewis, M.D., Rose Viscardi, M.D.

Industry Representative (non-voting):
Steven Ryder, M.D. – Acting Industry Representative

Advisory Committee for Reproductive Health Drugs Members Absent:
Charles Lockwood, M.D., Ronald S. Gibbs, M.D., Jonathan Tobert (Industry Representative)

Consultant (Government Employee) (non-voting)
Roberto Romero, M.D.

FDA Participants:
Julie Beitz, M.D., Dan Shames, M.D., Scott Monroe, M.D., Lisa Kammerman, Ph.D., Barbara Wesley, M.D.

Open Public Hearing Speakers:
Connie Lawson, Barbara Dehn, Michael Paidas, Nancy Green, Joseph Hwang, Terri Grossklaus, Jackie Duda, Davene White, and Cynthia Pearson

Issue:
The Committee discussed the safety and efficacy of New Drug Application (NDA) 21-945), proposed trade name Gestiva, 17 alpha-hydroxyprogesterone caproate injection, 250 mg/mL, Adeza Biomedical, for the proposed indication prevention of preterm delivery in women with a history of a prior preterm delivery.

The agenda proceeded as follows:

Call to Order and Introductions	Ezra Davidson, M.D. Acting Chair, Advisory Committee for Reproductive Health Drugs (ACRHD)
Conflict of Interest Statement	Teresa Watkins, PharmD. Designated Federal Official (ACRHD)
Welcome and Comments	Scott Monroe, M.D. Acting Director, Division of Reproductive and Urologic Drugs
FDA Invited Speaker	
Causes of Premature Birth: The Preterm Parturition Syndrome	Roberto Romero, M.D. Chief, Perinatology Research Branch Intramural Division, NICHD, NIH, DHHS
Sponsor Presentation	
17P for the Prevention of Recurrent Preterm Birth	Durlin E. Hickok, MD, MPH Vice President, Medical Affairs Adeza Biomedical
The Unmet Medical Need to Reduce Preterm Birth	Michael P Nageotte, MD Professor, Obstetrics and Gynecology University of California, Irvine

FDA Presentation

Efficacy and Safety Findings and Issues — Barbara Wesley, MD, MPH
Medical Officer
Division of Reproductive and Urologic Products

Clarifying questions from the committee to either FDA or Adeza

Open Public Hearing

Statistical Presentation — Daniel Gillen, Ph.D.
Assistant Professor,
Department of Statistics
University of California, Irvine

Committee Discussion

Committee vote

Questions to the Committee:

Adequacy of Clinical Data to Support Effectiveness

In general, the FDA requires an Applicant for a new drug product to submit two adequate and well-controlled clinical trials as substantial evidence of effectiveness. One of the circumstances in which a single clinical trial may be used as substantial evidence of effectiveness is a trial that has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome, and confirmation of the result in a second trial would be logistically impossible or ethically unacceptable. The Applicant is seeking marketing approval for 17-hydroxyprogesterone caproate (17OHP-C) based primarily on (1) the findings from a single clinical trial and (2) a surrogate endpoint for neonatal/infant morbidity and mortality (i.e., reduction in the incidence of preterm births at less than 37 weeks gestation).

Question 1 (The original Question 1b was split into 1b and 1c.)

a. Is the primary endpoint of Study 17P-CT-002 ─ prevention of preterm birth prior to 37 weeks gestation ─ an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity?

YES = 5
NO = 16
ABSTAIN = 0
TOTAL = 21

b. If not, would prevention of preterm birth prior to 35 weeks gestation be an adequate surrogate?

YES = 13
NO = 8
ABSTAIN = 0
TOTAL = 21

c. If not, would prevention of preterm birth prior to 32 weeks gestation be an adequate surrogate?

YES = 20
NO = 1
ABSTAIN = 0
TOTAL = 21

Question 2. Do the differences in the incidence of preterm birth in Study 17P-CT-002 prior to 37 weeks in the vehicle (control) group (**55%**) compared to those in the control arms of (a) another Maternal Fetal Medicine Units Network trial (approximately **37%**) and (b) Study 17P-IF-001 (**36%**) evaluating similar high risk populations indicate the need to replicate the findings of Study 17P-CT-002 in a confirmatory trial?

YES = 9
NO = 12
ABSTAIN = 0
TOTAL = 21

Question 3 (The original Question 3a was split into 3a and 3b. The original Question 3b was changed to 3c.)

a. **Do** the data reviewed by the Committee provide substantial evidence that 17OHP-C prevents preterm birth prior to 35 weeks gestational age?

YES = 12
NO = 9
ABSTAIN = 0
TOTAL = 21

b. Do the data reviewed by the Committee provide substantial evidence that 17OHP-C prevents preterm birth prior to 32 weeks gestational age?

YES = 7
NO = 14
ABSTAIN = 0
TOTAL = 21

NOTE: The tally was announced incorrectly at the meeting as 6 Yes, 15 No, 0 abstain.

c. Do the data reviewed by the Committee provide substantial evidence that 17OHP-C reduces fetal and neonatal mortality or morbidity?

YES = 2
NO = 19
ABSTAIN = 0
TOTAL = 21

Potential Safety Concern and Adequacy of Safety Data
There was a numeric increase in the percentage of second trimester miscarriages (pregnancy loss prior to Week 20 of gestation) and stillbirths in the 17-hydroxyprogesterone caproate group. Overall, 11 of 306 subjects (3.6%, 17OHP-C group) and 2 of 153 subjects (1.3%, vehicle group) had a second trimester miscarriage or stillbirth.

Question 4

a. Is further study needed to evaluate the potential association of 17OHP-C with increased risk of second trimester miscarriage and stillbirth?

YES = 21
NO = 0
ABSTAIN = 0
TOTAL = 21

b. If so, should this information be obtained prior to approval for marketing or post-approval?

PRE-APPROVAL = 8
POST-APPROVAL = 13
ABSTAIN = 0
TOTAL = 21

Question 5. Are the overall safety data obtained in Studies 17P-CT-002 and 17P-IF-001 and Study 17P-FU (long-term follow-up) adequate and sufficiently reassuring to support marketing approval of 17OHP-C without the need for additional pre-approval safety data?

YES = 13
NO = 8
ABSTAIN = 0
TOTAL = 21

Post-Approval Clinical Study(s)
Question 6

a. If 17-hydroxyprogesterone caproate were to be approved for marketing without additional pre-approval clinical studies, would you recommend that the Applicant conduct a post approval clinical trial(s) to investigate further safety or effectiveness?

YES = 21
NO = 0
ABSTAIN = 0
TOTAL = 21

b. If so, what would be the primary objective of the trial(s) (i.e., what unanswered question(s) would the study investigate)?

Although the following list is not all inclusive, it is representative of the committee participant responses. A full transcript will be posted to the FDA website in approximately 2 weeks.

-Further evaluation of mid-trimester loss and still births
-Further elucidation of the pharmacokinetic and pharmacodynamic properties of 17-hydroxyprogesterone caproate (17P).
-Exploration and optimization of mg/kg dosing
-Evaluation of the impact of increased blood volume on drug levels
-Further evaluation of carcinogenic potential
-Long term follow up studies of children exposed to 17P, including evaluation of reproductive health, fertility, and genital development
-Long term comparative studies of 17P exposed and non-exposed siblings.
-Evaluation of the effect of 17P on the development of gestational diabetes in the mother, as well as other maternal complications.
-Evaluation of the effect of 17P on length of hospital stay for the neonate.
-Evaluation of 17P potential to cause or exacerbate depression in the mother.
-Explore creating a registry to track events.
-Further efficacy studies.
-Exploration of 17P use for other indications

Adjournment at approximately 4:40 p.m.