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APPLICATION NUMBER:

21945Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-945
Priority or Standard	Priority
Submit Date(s)	12 July 2010
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Division / Office	Division of Reproductive and Urologic Products
Reviewer Name(s)	Barbara Wesley, M.D., M.P.H.
Review Completion Date	3 February 2011
Established Name	hydroxyprogesterone caproate
(Proposed) Trade Name	Makena
Therapeutic Class	Progestin
Applicant	Hologic Inc.
Formulation(s)	Injectable (Intramuscular - IM)
Dosing Regimen	250 mg (1 mL) weekly from between 16 weeks, 0 days, and 20 weeks 6 days to 37 weeks of gestation or until delivery
Indication(s)	Reduction of the Risk of Preterm Birth
Intended Population(s)	Pregnant women with a history of at least one spontaneous singleton preterm birth

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

As the primary reviewing Medical Officer for this application, I recommend an *approval action* under the Subpart H regulation (21 CFR 314.510) [also referred to as Subpart H] for 17α-hydroxyprogesterone caproate [hereafter referred to as 17-HPC, but also known as HPC and 17P] for the reduction of the risk of preterm birth (PTB) in women with a singleton pregnancy who have a history of a singleton spontaneous preterm birth. I make this recommendation because the Applicant has fully addressed the clinical deficiencies that are listed in the January 23, 2009 Complete Response letter to my satisfaction.

The Subpart H regulation states that:

"FDA may grant approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit…. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit".

The Applicant submitted a single phase 3 clinical trial which demonstrated a statistically strong ($p<.001$) reduction in the incidence of preterm births prior to 37 weeks gestation, the protocol pre-specified primary endpoint. There is recent evidence that "late preterm births" (births between $34^{0/7}$ and $36^{6/7}$), which comprise 71.3% of all preterm births, are increasing, and suffer greater neonatal and childhood morbidity and mortality than previously thought (Adams-Chapman 2006[1], Tomashek 2007[2], McIntire 2008[3], Martin 2009[4], The Consortium on Safe Labor 2010[5]). These data indicate that "preterm birth prior to 37 weeks" is "a surrogate endpoint that is reasonably likely to predict clinical benefit." As such, I find the evidence of benefit on this surrogate endpoint sufficient to support approval on the basis of a single clinical trial, with the requirement that an additional confirmatory trial be conducted under Subpart H, in order to evaluate the treatment benefit of 17-HPC on a clinical endpoint, specifically neonatal mortality and morbidity.

The reduction in preterm births at earlier gestational ages (i.e., <35 weeks and < 32 weeks), although statistically significant, did not meet the level of statistical significance generally expected to support approval of a drug product based on the findings from a single clinical trial.

1.2 Risk Benefit Assessment

Detailed descriptions of the submitted studies for this NDA and detailed risk benefit assessments are located in the primary Medical Officer's reviews from the previous two review cycles and in Section 2.5.2 of this review.

1.2.1 Efficacy

In support of the efficacy of 17-HPC, the original application (submitted on April 14, 2006) included data from one principal phase 3 active treatment clinical trial (Study 17P-CT-002; 463 subjects – 310 in the 17-HPC arm). The principal study was a double-blind, vehicle-controlled trial that randomized subjects 2:1 to 17-HPC or vehicle. Inclusion criteria were pregnant women with a history of a previous spontaneous singleton preterm birth, who were at a gestational age between 16 weeks-0 days (16^0) and 20 weeks-6 days (20^6) at randomization.

The primary efficacy endpoint was percent of births occurring at <37 weeks gestation. Additional endpoints, requested by the FDA, included percent of births at <35 weeks at <32 weeks gestation, and a composite index of neonatal morbidity and mortality.

The efficacy results from Study 17P-CT-002 are summarized in Table 1 below.

Table 1 Proportion of Subjects with Delivery at <37^0, <35^0, and <32^0 Weeks

Data Source	17-HPC (N=310)	Vehicle (N=153)	Mean Treatment Differences and 95% Confidence Interval[A]
	%	%	
<37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
<35^0 weeks	21.3	30.7	-9.4% [-18.7%, -0.4%]
<32^0 weeks	11.9	19.6	-7.7% [-16.1.%, -0.3%]
Composite Neonatal Morbidity Score[B]	11.9	17.2	0.1194 (nominal P value)

[A] The confidence intervals, based on a t-test, are adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, the final p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

[B] The composite neonatal morbidity measure counted any liveborn infant who experienced death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC. P-values have not been adjusted for multiple comparisons.

Source: FDA statistical analysis of Applicant's data from Study 17P-CT-002 and Applicant's analysis.

The proportion of babies with at least one event on the composite index of neonatal morbidity/mortality was lower in the 17-HPC group ([11.9%], 35/295 infants) than in the vehicle group ([17.2%], 26/151 infants) but the between-group difference was not statistically significant.

The strength of the efficacy data relies on statistically significant reductions of PTB at <37, < 35 and < 32 weeks gestation. The surrogate endpoints of reductions of PTB at < 35 and < 32 weeks were thought by an Advisory Committee to predict a reduction in neonatal mortality and morbidity. At the time of the Advisory Committee meeting in 2006, the endpoint of PTB at < 37 weeks was not believed to be an adequate surrogate for neonatal outcome. However, there is recent evidence that "late preterm births" ($34^{0/7}$ to $36^{6/7}$ weeks gestation), which comprise 71.3% of all preterm births, and "early term births" ($37^{0/7}$ to $38^{6/7}$ weeks gestation) suffer greater neonatal and childhood morbidity and mortality than previously thought (Adams-Chapman 2006[6], Tomashek 2007[7], McIntire 2008[8], Martin 2009[9], The Consortium on Safe Labor 2010[10]). The Advisory Committee was primarily supportive of approving this drug, with the stipulation

that another confirmatory clinical trial will be conducted for further demonstration of safety and efficacy.

1.2.2 Safety

The primary source of safety data in the application was obtained from the primary efficacy and safety trial (Study 17P-CT-002) and a follow up safety study (Study 17P FU) conducted on the children of the mothers who participated in Study 17P-CT-002. Additional supportive safety data were obtained from an initial active treatment clinical trial (Study 17P-IF-001) that was similar in design to Study 17P-CT-002, but was terminated prematurely due to recall of the study drug due to potency concerns.

Listed below are the overall safety results from study 17-CT-002:

- There were *no definitive significant safety signals identified.*
- There was a trend toward an increased risk of miscarriage and stillbirths in the 17-HPC treatment arm and a trend toward a decrease in neonatal death, with *no overall net survival benefit* (see Table 2).

Table 2 Miscarriages, Stillbirths, and Neonatal Deaths

Pregnancy Outcome	17-HPC N=306 n (%)	Placebo N=153 n (%)	Nominal P-value [A]
Miscarriages <20 weeks gestation	5 (1.6)	0	0.1746
Stillbirth	6 (2.0)	2 (1.3)	0.7245
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.1159
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.6887**

[A] No adjustment for multiple comparisons.
Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

- In Studies 17P-CT-002 and 17P-IF-001, there was a suggestion that 17-HPC may impair glucose tolerance; this warrants further study. Also based on trends in these studies, there is reason to further study the effects of 17-HPC on amniotic fluid levels and preeclampsia.
- Injection site pain, swelling and pruritus were the most common adverse reactions (ARs) and reasons for discontinuation in study 17-CT-002.

The results of the NICHD MFMU Network follow-up Study 17P-FU is summarized below in Table 3:

Table 3 Development Delay in Children from Study 17P-CT-002 *

ASQ Area of Development below Cutoff	17OHP-C n = 13 (6.7%)	Vehicle n = 8 (9.8%)
	Percent Affected	
Communication	4.7	8.5
Gross motor	1.6	2.4
Fine motor	5.2	3.6
Problem solving	2.6	6.1
Personal-social	2.6	1.2

* Includes only children who had an ASQ score compatible with a developmental delay and an independent diagnosis of developmental delay by a professional.
Source: Final study report : Study 17P-FU

There were no signals of developmental delay in the follow-up study of children.
The ASQ was completed for 275 children, 193 from the 17OHP-C group and 82 from the vehicle group. The age of the children at the time of completion of the ASQ ranged from 30 to 64 months; mean age at time of completion did not differ between the 17OHP-C and vehicle groups (47.2 vs. 48.0 months).

Use of compounded 17-HPC:
Finally, of significant concern, is the fact that several national surveys have indicated that a large number of obstetricians currently treat pregnant women with compounded 17-HPC, which is not available as an FDA-regulated, Good Manufacturing Process (GMP)-produced product.

1.2.3 Summary

The applicant submitted a single phase 3 clinical trial in 2006 that demonstrated a statistically strong reduction in the incidence of preterm births prior to 37 weeks gestation, the protocol pre-specified primary endpoint. The strength of the efficacy data in Study 17P-CT-002 relies on the statistically significant reduction of PTB at <37 weeks gestation. The reduction in preterm births at earlier gestational ages (i.e., <35 weeks and < 32 weeks), although statistically significant, did not meet the level of statistical significance generally expected to support approval of a drug product based on the findings from a single clinical trial. The findings from this single study alone, based on a surrogate endpoint, were not sufficiently persuasive to support approval without the addition of further confirmatory clinical data that includes an appropriately powered clinical endpoint of neonatal morbidity and mortality. As such, I find the evidence of benefit on this surrogate endpoint sufficient to support approval on the basis of a single clinical trial, with the requirement that an additional confirmatory trial be conducted under Subpart H, in order to evaluate the treatment benefit of 17-HPC on a clinical endpoint, specifically neonatal mortality and morbidity.

The surrogate endpoints of reductions of PTB at < 35 and < 32 weeks were thought by an Advisory Committee to predict a reduction in neonatal mortality and morbidity. However, there is recent evidence that "late preterm births," ($34^{0/7}$ to $36^{6/7}$ weeks gestation), which comprise

71.3% of all preterm births, and "early term births ($37^{0/7}$ to $38^{6/7}$ weeks gestation) suffer greater neonatal and childhood morbidity and mortality than previously thought at the time of the original submission of this application and the advisory committee meeting.

There is currently no approved treatment to reduce the risk of preterm birth in pregnant women. Many clinicians are using compounded HPC in an attempt to reduce the risk of preterm birth.

The statistical strength of the reduction in preterm births at <37 wks ($p< 0.001$) is sufficient to support approval of this NDA on the basis of a single trial. However, because the current trial relies upon a surrogate endpoint, this reviewer is recommending approval of this NDA under Subpart H, with the stipulation that another confirmatory clinical trial should be completed for further demonstration of a treatment benefit on a clinical outcome.

The Applicant has initiated the required confirmatory study and has addressed to my satisfaction the clinical deficiencies that were listed in the January 23, 2009 Complete Response letter.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Since 17-HPC is being approved for marketing under the Subpart H regulation, one phase 4 requirement is completion of the confirmatory safety and efficacy study. The infant follow-up study will also be required as a postmarketing requirement (PMR). Characterization of the PK profile of 17-HPC in pregnant women through different stages of gestations and evaluation of the effects of 17-HPC on cytochrome metabolic activity (an *in vitro* study in human hepatocytes) will be requested as postmarketing commitments.

The Applicant has agreed on January 14, 2011 to the following timelines for the PMRs:

PMR #1722-1: To complete the clinical trial of hydroxyprogesterone caproate (HPC) in women with a singleton pregnancy who had a previous spontaneous preterm birth (Protocol #17P-ES-003):

Revised Protocol Submission	March 2011
Trial Completion	June 2016
Final Report Submission	December 2016

PMR #1722-2: To complete the clinical follow-up study (Protocol #17P-FU-004) of children born to women who participated in Protocol #17P-ES-003:

Revised Protocol Submission	March 2011
Final Interim Report Submission	December 2016
Study Completion	July 2018
Final Report Submission	October 2018

The Applicant also agreed on January 14, 2011 to conduct the following trials and studies as postmarketing commitments, according to the specified timelines:

PMC #1722-3: Submission of an academic publication of pharmacokinetic data on hydroxyprogesterone caproate and its metabolites in plasma and urine of pregnant women throughout different stages of gestation.

Final Report Submission: December 2011

PMC #1722-4: If the publication listed in the above postmarketing commitment is not submitted by December 31, 2011 or if the results from the publication do not include all the relevant findings (e.g., urinary metabolites), the Applicant will conduct the following clinical trial: a non-randomized clinical pharmacokinetic trial of hydroxyprogesterone caproate and its metabolites in pregnant women. This trial will provide data characterizing the pharmacokinetics of hydroxyprogesterone caproate and its metabolites in plasma and urine throughout the different gestational stages.

Final Protocol Submission: June 2012
Trial Completion: June 2014
Final Report Submission: November 2014

If the publication in support of postmarketing commitment 1722-3 is submitted on time and deemed adequate, then postmarketing commitment 1722-4 may be released.

PMC #1722-5: An *in vitro* study in human hepatocytes to determine whether hydroxyprogesterone caproate induces or alters the metabolic activities of CYP1A2, CYP2A6 and CYP2B6:

Final Protocol Submission: June 2011
Study Completion: March 2012
Final Report Submission: July 2012

2 Introduction and Regulatory Background

2.1 Product Information

The proposed dosing regimen is a weekly intramuscular injection of 250 mg of 17-HPC in 1 mL castor oil with 46% benzyl benzoate and 2% benzyl alcohol, beginning at 16 weeks 0 days (16^0) to 20 weeks 6 days (20^6) weeks gestation and used through 36^6 weeks gestation or birth.

17-HPC is a clear, yellow, sterile, non-pyrogenic solution for intramuscular injection. Each 5 mL vial contains 17 α-hydroxyprogesterone caproate for injection USP, 250 mg/mL (25% w/v), in castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently there is no drug product approved in the United States *to reduce the risk of preterm birth*; however, 17-HPC is compounded by pharmacists and is used widely for this indication in women at high risk. The medical need for an approved drug product to reduce the risk of preterm birth is particularly acute because there also are no approved drug products currently marketed in the United States for the treatment of preterm labor. Although several drug products with tocolytic properties (i.e., stopping uterine contractions) are used off-label for *treatment* of preterm labor, randomized controlled trials have failed to demonstrate that these drugs improve perinatal outcomes.

Use of Compounded 17-HPC

17α-hydroxyprogesterone caproate is compounded by pharmacists and is used widely for prevention of preterm birth in women in the U.S. In addition, clinicians are also using other forms of progesterone, approved for other indications, to prevent preterm birth.

Two mail surveys were sent to all board certified Maternal-Fetal Medicine (MFM) sub-specialists in the United States to evaluate the use of "progesterone" to prevent preterm birth: The objective of the first study (Ness 2006[11]) was to determine the current prescription of progesterone to prevent preterm birth (PTB) among board-certified maternal-fetal medicine (MFM) specialists in the United States. A survey was sent to examine their prescription of and attitudes regarding progesterone (several preparations) to prevent PTB 6 months following publication of the National Institute for Child Health and Human Development trial (Study 17P-CT-002). Of 1,264 questionnaires sent, 526 were returned (response rate, 42%). One hundred ninety-eight (38%) respondents prescribed progesterone, and 324 (62%) did not. *Most non-prescribers were awaiting more data and were more concerned than were prescribers about long-term effects ($p < 0.0001$). Twenty percent of prescribers prescribed progesterone for women with current signs or symptoms of preterm labor.*

The purpose of the follow-up study (Bailit 2007[12]) was to determine whether current attitudes regarding the use of progesterone to prevent preterm birth have changed since their last survey in 2003. They mailed a 20-question survey to 1264 board-certified Maternal-Fetal Medicine specialists in the United States between February and March of 2005 asking about their use and attitudes regarding progesterone to prevent preterm birth. Five hundred and seventy-two surveys were returned (response rate of 45%). In 2005, 67% of respondents used progesterone to prevent SPTB, compared to 38% in 2003 ($P < 0.001$). *Among users, 38% recommended progesterone for risk factors other than previous SPTB. Users were more concerned about lack of insurance coverage compared to nonusers but nonusers were more concerned about safety, efficacy, need for more data, and long-term neonatal effects.*

Medical Officer's Comments:

- *These data illustrate that there is an increasing trend to use progesterone to prevent preterm birth, despite persistent concerns about insufficient data and patient-perceived significant safety concerns and lack of an FDA-approved product.*
- *Providers have been willing to treat women who do not meet the "accepted risk factor for the proposed indication" – women with a previous preterm birth. A well-defined description of the population for whom safety and efficacy data are available will be provided in the 17-HPC package labeling, which may help to address this problem.*

2.3 Availability of Proposed Active Ingredient in the United States

In 1956, the FDA approved the marketing of hydroxyprogesterone caproate (NDA 10-347, Delalutin), for the treatment in pregnant women of habitual and recurrent abortion, threatened abortion, and post-partum "after pains," and for the following indications in non-pregnant women: amenorrhea, dysfunctional uterine bleeding, disturbances of the menstrual cycle, deficiency syndromes, dysmenorrhea, premenstrual tension, and cyclomastopathies. In addition, the drug was indicated for the production of secretory endometrium and desquamation and for the suppression of gonadotropic hormone production and ovulation. This approval was based largely on review of safety, in that it occurred prior to the FDA Drug Amendment of 1962, which required that drugs must have substantial evidence of efficacy in addition to evidence of safety in adequate and well-controlled trials.

In 1972, the FDA approved the marketing of 17-HPC for an indication of advanced adenocarcinoma of the uterine corpus (stage III or IV) (NDA 16-911, Delalutin).

In 2000, the FDA withdrew approval for Delalutin. This action was taken at the request of the holder of the NDA because the holder was no longer marketing the drug. The Federal Register (Vol. 75, No. 122/Friday, June 25, 2010/Notices) states "The Food and Drug Administration (FDA) has determined that DELALUTIN (hydroxyprogesterone caproate) injection, 125 milligrams (mg)/milliliter (mL) and 250mg/mL, was not withdrawn from sale for reasons of safety or effectiveness." 17-HPC for injection is currently being compounded by pharmacists in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

2.4.1 Castor Oil

Rare post-marketing reports from outside the U.S. describe an immediate post-injection reaction characterized by transient symptoms that include urge to cough, coughing spells, dyspnea and respiratory distress, occurring immediately after the deep gluteal injection of 4 mL of an oily solution of testosterone undecanoate in castor oil. It is postulated that these reactions are due to the phenomenon of pulmonary oil microembolism (POME) that can occur following direct

vascular or lymphovascular delivery of oil-based preparations, which then reach the lung as the first "filtering" organ for venous return circulation and right heart output. POME has not been described in preparations that contain less than 4 mL of castor oil, although cough reactions have rarely been reported with marketed oily depot hormone preparations having a volume of 1 or 2 mL.

Medical Officer's Comments:

- *There is virtually no risk of POME with the volume of only 1 ml of castor oil to be delivered for 17-HPC; however, the Applicant has agreed to monitor the subjects in the Confirmatory study for coughing and shortness of breath post-injection.*

2.5 Summary of Previous Regulatory Activity

2.5.1 Pre-NDA Activity

The use of 17-HPC for the prevention of recurrent preterm birth was investigated by the National Institute of Child Health and Development (NICHD), Maternal Fetal Medicine Units (MFMU) Network, which at that time consisted of 19 university-based clinical centers in the U.S. After this data was published in the New England Journal of Medicine (Meis et al., 2003[13]), the then-Applicant, Adeza Biomedical, met with the Division of Reproductive and Urologic Products (hereafter referred to as the Division) to discuss the possibility of using this data as the basis for an NDA for 17-HPC for the indication of prevention of preterm birth. This clinical trial, however, was not originally intended for drug approval purposes.

The Division conveyed several concerns and recommendations to the Applicant during this and subsequent meetings. These included the following:

- A major concern was the lack of follow-up data, beyond the period of initial hospital assessment, of babies of mothers who had received 17-HPC for the prevention of preterm birth. The Division requested that the Applicant obtain follow-up data on children through at least 2 years of age.
- A second major concern related to the drug product(s) used during the trial. The Applicant was informed that complete chemistry, manufacturing and control (CMC) information would need to be provided about the drug product, including its purity and potency. The Applicant will need to ensure that the drug product used in the NIH sponsored clinical trial and the to-be-marketed formulation will be identical, or appropriately bridged.

- The Division had some concerns about the efficacy endpoints of Study 17P-CT-002 and the adequacy of these endpoints to support approval of a new drug product for marketing in the U.S, particularly because the proposed NDA supporting the safety and effectiveness of 17-HPC was based primarily on the outcome of a single clinical trial. These concerns included:
  - The lack of any improvement in overall mortality, and only a suggestion of an improvement in overall neonatal morbidity in offspring of the 17-HPC treated subjects compared to the placebo treated subjects.
  - Clinical Trial 17P-CT-002 did not show strong statistical significance for the endpoints of reducing the number of births at gestational ages <35 and <32 weeks, gestations when infant morbidity/mortality is a much greater clinical problem. The Division, however, recognized that the trial was not powered for these endpoints.
  - The primary endpoint (preterm birth < 37 weeks gestation) of Clinical Trial 17P-CT-002 was a surrogate for pregnancy outcome (neonatal/infant morbidity and mortality). The Division indicated that its review would also consider what it believed to be the most important outcomes (overall survival of fetuses/infants and a significant reduction in serious morbidities from the time of enrollment) rather than relying on merely an increase in gestational age, without other accompanying clinical benefits.
  - Normally, either two adequate and well-controlled studies or a single study with a robust and compelling outcome and strong supporting data would be required to support approval of a new drug product. There was a possibility that the data from Trial 17P-CT-002 would not be sufficient to demonstrate that 17-HPC is safe and effective for the prevention of preterm birth.

2.5.2 Regulatory Summary and NDA Actions

NDA 021945 was first submitted to the Division of Reproductive and Urologic Products (DRUP) in April 2006. The Applicant's original proposed indication was the use of 17-HPC for the *prevention of preterm birth in women with a prior history of at least one spontaneous preterm birth.* The clinical component of NDA 021945 was based largely on the data from the NICHD clinical trial (Study 17P-CT-002) and a follow-up safety study (Study 17P-FU) that enrolled children whose mothers had participated in Study 17P-CT-002. Following a priority review of NDA 021945, which included discussion of the NDA at the August 2006 Advisory Committee for Reproductive Health Drugs (ACRHD), the Application received an Approvable Action in October 2006. The Application was not approved because of clinical, nonclinical toxicology, and chemistry, manufacturing and control (CMC) deficiencies.

In April 2008, the Applicant submitted the first Complete Response. In the Complete Response, the Applicant adequately addressed the nonclinical toxicology and CMC deficiencies, but did not adequately address the clinical deficiencies. The Applicant did not provide sufficient documentation that the proposed confirmatory clinical trial, which would be required to support

approval of the NDA under Subpart H regulations for accelerated approval, was feasible and was likely to be completed successfully. On January 23, 2009, DRUP issued another Complete Response Letter.

In the current submission (the second Complete Response), the Applicant satisfactorily addressed the 2 clinical deficiencies listed in the Division's Complete Response Letter of January 2009. In regard to the first deficiency, the Applicant has provided the requested documentation that the confirmatory safety and efficacy trial (Study 17P-ES-003) has been initiated at both US and non-US sites and has enrolled more than 5% of the planned 1,700 subjects. In regard to the second deficiency, the Applicant had previously submitted an acceptable protocol (Study 17P-FU-004) for developmental assessment at ages 18-24 months of children whose mothers had participate in Study 17P-ES-003. The current submission does not include any new nonclinical, CMC, or clinical pharmacology data. During the current review cycle, it was decided on January 4, 2011, to treat this Application as if it were an NDA for a new molecular entity (NME) because of (1) the long period that has elapsed since HPC was last marketed as a FDA-approved drug product in the US and (2) the complexity of the review issues. As such, the signatory authority for this NDA has been transferred to the Office of Drug Evaluation III.

List of NDA Actions by the FDA and Complete Responses by the Applicant

First Action by the FDA

On 20 October 2006 the FDA sent the Applicant an Approvable Letter for hydroxyprogesterone caproate for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth. The Applicant was asked to address the following clinical deficiencies:

1. "Further study is needed to provide confirmatory evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly, or through a well-established surrogate, such as the rate of preterm birth prior to 35 and 32 weeks of gestation.
2. There are insufficient data to evaluate a potential association of hydroxyprogesterone caproate (HPC) with increased risk of early fetal loss (second trimester miscarriage and stillbirth)".

The Division required the following information from the Applicant to address the clinical deficiencies:

1. "Submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of HPC for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510. If a placebo-controlled trial is determined not to be feasible, provide alternative study design proposals.

2. Provide a draft protocol to evaluate the potential association of HPC with increased risk of second trimester miscarriage and stillbirth. This could be assessed as a part of the confirmatory efficacy study referred to in Item No. 1 above.

Additional clinical issues that would need to be addressed postmarketing, if the product were to be approved:

1. "Completion of the additional efficacy and safety study(ies) requested above under the description of clinical deficiencies will be required as a condition of an approval under Subpart H 21 CFR 314.510 (Item No. 1 above under clinical deficiencies) or as a formal phase 4 commitment (Item No. 2 above under clinical deficiencies).
2. Long-term post treatment safety data (at least through puberty) from children whose mothers had been treated with HPC is lacking in the NDA. This information is requested and could be obtained through the establishment of a surveillance program (e.g., registry) to evaluate the effects of prenatal exposure in adolescents and young adults. Submit your proposal as to how these data would be obtained.
3. Additional developmental assessment is needed of children at ages 18-24 months whose mothers had been treated with HPC. This assessment could be obtained from the offspring of women enrolled in the confirmatory efficacy study or the safety study addressing early fetal loss. Children who screen positive for developmental delay should have a formal psychometric assessment and an additional assessment by a neurologist".

First Complete Response Submitted by the Applicant

The Applicant submitted a draft protocol for study 17-ES-003 entitled "A Multi-Center, Randomized, Double-Blind Study of 17-α-Hydroxyprogesterone Caproate (17-P) versus Placebo for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous Preterm Delivery," on January 15, 2009. In a letter to the Applicant on 12/17/2009, the Division agreed with the design of this Protocol (hereafter referred to as the "Confirmatory Study"). This study is designed to:

1. Confirm one of the previous findings of efficacy in Study 17P-CT-002 (i.e., a reduction in preterm births at $< 35^0$ weeks of gestation),
2. Obtain further information regarding the effect of treatment with hydroxyprogesterone caproate (HPC) on neonatal morbidity and mortality, and
3. Address the concern regarding early pregnancy loss identified in our Approvable letter of October 20, 2006.

In addition, the Applicant provided a protocol for a follow-up study of offspring up to two years of age in the U.S. and in other countries. The Division conveyed their preliminary agreement with this protocol to the Applicant on 17 December 2009. See Sections 6 and 7 for a complete description of the protocols for Studies 17P-ES-003 and 17P-FU-004

However, the Applicant was unable to provide adequate documentation that it would be feasible for them to conduct and successfully complete the Confirmatory Study. The American College

of Obstetrics and Gynecology (ACOG) issued Committee Opinion No. 419 (ACOG Committee on Obstetric Practice, "Use of progesterone to reduce preterm birth," (October 2008[14]). Despite the lack of additional evidence for efficacy of 17-HPC, (or any other progesterone for this indication), this document states "*Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes."*

This sentence is unambiguous, and has been interpreted as an attempt to create a standard of care. A lack of documentation by the health care provider regarding such counsel for women with this risk of PTB can potentially be considered inadequate or substandard care. This reviewer was concerned that health care providers and Institutional Review Boards, particularly in the U.S., might be reluctant to conduct randomized, placebo controlled trials of 17-HPC for PTB prevention as a result of this ACOG Committee Opinion. This opinion raised my concern that successful completion of the placebo-controlled study that was proposed was not likely to be feasible if the trial is conducted primarily in the U.S. I believed that the ACOG opinion virtually established offering treatment with progesterone to such high-risk patients as a *de facto* standard of care. Institutional Review Boards (IRBs) and patients might interpret the ACOG committee opinion as indicating that any remaining questions regarding the efficacy and safety of hydroxyprogesterone caproate are not sufficient to justify conducting a placebo-controlled study. The Division agreed that adequate assurance of feasibility could only be addressed by actual initiation of the trial.

Second Action by the FDA

The FDA sent another Action (Complete Response) Letter to the Applicant on 23 January 2009 that defined additional information required to obtain approval to market 17-HPC (referred to as HPC in the letter). The letter stated that resolution of the clinical deficiencies would require the following:

1. The Confirmatory Study will need to enlist investigators at a sufficient number of U.S. and non-U.S. sites to support target enrollment of 1,700 subjects; no site should enroll more than 15% of the total number of subjects. Acceptable documentation of feasibility would include the following elements:

- Documentation of IRB approval for at least 15 investigational sites (including U.S. and non-U.S. sites).
- Enrollment of at least 5% of the total anticipated sample size.
- Enrollment of at least 15 subjects at U.S. study sites.
- Agreement (with supporting evidence) to enroll at least 10% of the total sample of 1,700 subjects from U.S. and Canadian sites.

2. Submit a final clinical protocol for a study that will provide additional data to address whether treatment of mothers with hydroxyprogesterone caproate has a detrimental effect on early infant/child development. For those children whose initial screening examination suggests a

developmental delay, the protocol should include formal psychometric and developmental assessments as well as an assessment by a pediatric neurologist."

Second Complete Response Submitted by the Applicant

On 12 July 2010, the Applicant submitted a second complete response containing the following information to address the recommendations in the Complete Response Letter:

The Applicant initiated a confirmatory randomized placebo controlled trial in pregnant women with a single gestation and a history of at least one spontaneous preterm birth (Study 17P-ES-003, under IND 68,108) on 12 November 2009.

- A total of 72 investigational sites have received Institutional Review Board (IRB)/ Ethics Committee (EC) approval from 40 separate IRB/ECs: 16 IRBs in the US; 24 ECs outside of the U.S.
- Currently 5.2% (89 patients) of the anticipated sample size of 1,700 patients has been randomized in the confirmatory clinical study; 82 subjects at U.S. study sites have been randomized. The goal for U.S. enrollment is 170 (10% of the total).
- The final clinical protocol for the infant follow-up study (17P-FU-004) was submitted as part of IND 68,108. The study will assess 350 children at an adjusted age of 24 months by the use of the ASQ-3 instrument with further evaluation of children with at least one positive domain with both a Bayley and neurological examination.

Medical Officer's Comments:

- *The Applicant has hired a contract research organization to provide support in recruiting patients*.
- *The Applicant has recruited a diverse group of U.S. sites, including academic centers, military medical centers and private practices, and it is anticipated that half of all sites will be in the U.S. and Canada.*
- *I believe the applicant has adequately demonstrated their ability to enroll sufficient numbers of patients to complete this study.*

2.5.3 Studies to Support NDA 21-945 (Original NDA Submission April 14, 2006)

The results of the NICHD research (Trial 17P-CT-002) formed the clinical basis of the New Drug Application (NDA) 21-945, which was submitted to the Food and Drug Administration (FDA) on 14 April 2006.

In support of their application for the use of 17-HPC for the prevention of preterm birth, the then-Applicant (Adeza Biomedical) also submitted data from an earlier active treatment clinical trial (Study 17P-IF-001) and a follow-up safety study of the offspring of mothers in Study 17P-CT-002 (Study 17P-FU).

Initial Formulation Study (Study 17P-IF-001)

This NICHD study began in February 1998, but treatment was terminated in March 1999 because the active study drug (17-HPC) was recalled by its manufacturer, under the direction of the FDA, due to violations of manufacturing practices potentially affecting the potency of the drug. At the time of termination, only 150 of the proposed 500 subjects had been randomized, and no data analysis had been done. Eighty six (86) subjects completed the treatment regimen before the study was stopped: 57 17-HPC subjects and 29 vehicle subjects. The study drug used in this prematurely terminated study is referred to as the Initial Formulation (IF). Information from this study was considered to be of limited value in supporting either the safety or efficacy of 17-HPC.

Principal Safety and Efficacy Trial (Study 17P-CT-002)

The principal study was a double- blind, vehicle-controlled trial that randomized subjects 2:1 to 17-HPC or vehicle. Inclusion criteria were pregnant women with a history of a previous spontaneous singleton preterm birth, who were at a gestational age between 16^0 and 20^6 weeks at randomization. The main exclusion criteria included: a known major fetal anomaly; prior progesterone or heparin treatment in the current pregnancy; a history of thromboembolic disease; and maternal medical/obstetrical complications (hypertension requiring medication, or a seizure disorder). Study medications were 17-HPC (250 mg/mL) in castor oil/vehicle. The dosing regime was a 250 mg weekly injection of 17-HPC, or 1 mL vehicle, beginning on the day of randomization through 36^6 weeks gestation, or delivery, whichever occurred first.

Efficacy

The pre-specified primary efficacy endpoint was percent of births at <37 weeks gestation. Additional endpoints, requested by the FDA, included percent of births <35 weeks and <32 weeks gestation, and a composite index of neonatal morbidity/mortality. The composite was based on the number of infants who experienced any one of the following: death; respiratory distress syndrome (RDS); bronchopulmonary dysplasia (BPD); grade 3 or 4 intraventricular hemorrhage (IVH); proven sepsis; or necrotizing enterocolitis (NEC).

This study was designed to enroll 500 subjects; however, because the pre-specified stopping criterion for efficacy was attained at an interim analysis, only 463 subjects were randomized and treated with study medication: 310 in the 17-HPC arm and 153 in the vehicle arm. Twenty seven (27) subjects withdrew from treatment in the 17-HPC arm vs. 14 in the vehicle arm, but remained in the study for determination of outcome. In the 17-HPC arm, seven withdrew due to an adverse event, compared to three in the vehicle arm. Four subjects were lost to follow-up, all in the 17-HPC arm.

The major efficacy findings from Study 17P-CT-002 are summarized in section 1.2 in the executive summary above and in Table 4 below. The results of other studies in the literature provide further support for the effectiveness of 17-HPC for prevention of PTB; however, the small sizes and variable entry criteria for these studies limit the strength of their findings. A detailed review of these studies can be found in the primary Medical Officer's review in the first

cycle on Oct. 18, 2006.

Table 4 Proportion of Subjects with Delivery at <37^0, <35^0, <32^0, and <28^0 Weeks

Data Source	17-HPC (N=310)	Vehicle (N=153)	Mean Treatment Differences and 95% Confidence Interval[A]
	%	%	
<37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
<35^0 weeks	21.3	30.7	-9.4% [-18.7%, -0.4%]
<32^0 weeks	11.9	19.6	-7.7% [-16.1.%, -0.3%]
Composite Neonatal Morbidity/Mortality Score[B]	11.9	17.2	0.1194 (nominal P value)

[A] The confidence intervals, based on a t-test, are adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, the final p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

[B] The composite neonatal morbidity measure counted any liveborn infant who experienced death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC. P-values have not been adjusted for multiple comparisons.

Source: FDA statistical analysis of Applicant's data from Study 17P-CT-002 and Applicant's analysis.

Neonatal mortality was numerically lower in the 17-HPC group, but the between-group difference was not statistically significant (2.6% vs. 5.9%). The composite index of neonatal morbidity/mortality was lower in the 17-HPC group (11.9%, 35/295 infants) than in the vehicle group (17.2%, 26/151 infants) but the between-group difference was also not statistically significant.

The proportion of infants with a birthweight < 2500 g, corresponding approximately to < 37 weeks gestational age, was statistically significantly lower in the 17-HPC arm (27.2%, [82/301] vs. 41.1% [62/151] in the vehicle arm). The numbers with a birthweight < 1500 g, corresponding approximately to < 32 weeks gestation, was numerically, but not statistically significantly lower in the 17-HPC arm (8.6% vs. 13.9% in the vehicle arm). The prolongation of pregnancy, defined as the time from randomization to delivery or date last pregnant, was numerically longer, by a mean of six days, in the 17-HPC group compared to the vehicle group. The mean gestational age at delivery was one week greater in the 17-HPC group compared to the vehicle group (36.2 vs. 35.2 weeks, p=0.031).

Medical Officer's Comments:

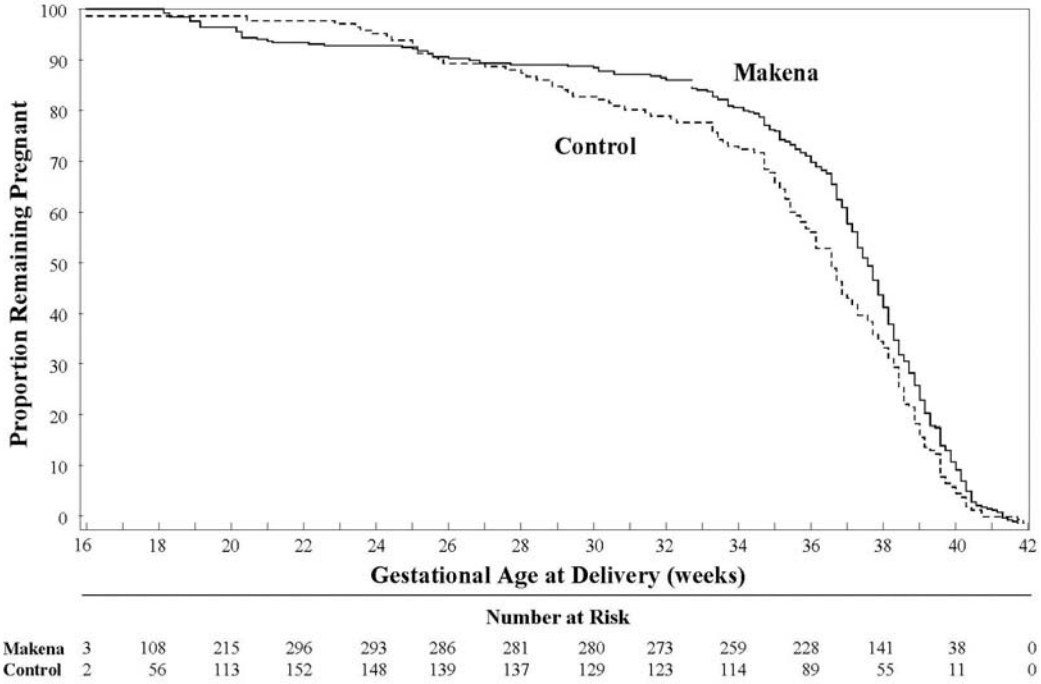
- *The strength of the efficacy data relies on statistically significant reductions of PTBs at <37, < 35 and < 32 weeks gestation. The reduction of PTB at < 37 weeks was the pre-specified surrogate endpoint and showed a statistically persuasive finding (p<0.001) of reduction in PTB. Despite the problems illustrated in the statistical review, I think the findings are sufficient to support approval on the basis of a single clinical trial. The Advisory Committee thought that PTB < 35 weeks and < 32 weeks gestation were adequate surrogate endpoints to predict neonatal mortality and morbidity; however,*

there is recent evidence that "late preterm births" (births between $34^{0/7}$ and $36^{6/7}$), which comprise 71.3% of all preterm births, are increasing, and suffer greater neonatal and childhood morbidity and mortality than previously thought. (see section 1.2.1 above).

- *The significant reduction in low birth weight and the prolongation of pregnancy by about 1 week adds further support that the significant reduction in PTB <37 weeks is accurate.*

The proportion of women remaining pregnant in Study 17-CT-002 as a function of gestational age is shown in Figure 1 below. Prior to approximately 25 weeks gestation, a numerically greater proportion of subjects randomized to the HPC group delivered prematurely; after 28 weeks gestation, a greater proportion of subjects randomized to the vehicle group delivered prematurely.

Figure 1Proportion of Women Remaining Pregnant as a Function of Gestational Age (Study 17P-CT-002)



Source: Applicant's submission of July 20, 2006, and to-be-approved Physician Labeling.

Medical Officer's Comments:

- *After adjusting for time on study drug, 7.5% of 17-HPC-treated subjects delivered prior to 25-weeks gestation compared to 4.7% of controls subjects. Whether treatment with 17-HPC contributed to these early pregnancy losses is not known and will be investigated further in the Applicant's ongoing post-approval trial.*
- *The mean gestational age at delivery for subjects with available outcome data was one week greater in the HPC group (36.2 weeks vs. 35.2 weeks). The median prolongation of pregnancy (defined as the time from randomization until delivery or date that the subject was*

last confirmed to be pregnant) was higher in the HPC group compared to the vehicle group (131 days vs. 125 days).

The number of subjects enrolled at each of the 19 study centers is listed in Table 5. Almost 30% of the subjects (126 of 463) were enrolled at a single center – University of Alabama.

Table 5 Enrollment of Subjects by Study Center

Center #	Name	# Enrolled
8	**University of Alabama**	**126**
4	University of Tennessee	45
20	University of Utah	43
18	University of Texas Southwestern	39
2	University of Pittsburgh	36
15	Ohio State University	28
9	Wayne State University	24
21	Thomas Jefferson University	24
13	Wake Forest University	22
11	University of Cincinnati	13
19	University of Texas San Antonio	13
17	University of Miami	11
23	Columbia University	11
14	University of Chicago	7
25	Case Western University	6
22	Brown University	5
26	University of Texas Houston	4
27	University of North Carolina, Chapel Hill	4
28	Northwestern University	2

Source: Table 1, 17P-CT-002 Final Study Report.

Medical Officer's Comment:

- *The disproportionately high enrollment at the University of Alabama site is of some concern to this reviewer. This disparity in enrollment numbers can potentially negate to some extent the balance one expects in a multicenter trial.*

To investigate further the effect of the Alabama site on the overall outcomes an additional analysis was performed in which the effect of the Alabama site was explored (see Table 6) There was consistency in the reduction of PTB across centers at < 37 weeks and < 35 weeks gestation; however, at < 32 weeks there was a greater reduction of PTB in the 17-HPC arm relative to vehicle at the University of Alabama compared to all other sites combined.

Table 6 Effect of Center on Proportion of Preterm Births at Weeks <37, <35, and <32

	University of Alabama			All Other Centers Combined			All Centers		
Data Source	17-HPC[a] (n=86) %	Vehicle (n=40) %	% PTB decrease	17-HPC[a] (n=224) %	Vehicle (n=113) %	% PTB decrease	17-HPC[a] (n=310) %	Vehicle (n=153) %	% PTB decrease
<37 weeks	26.7	45.0	-18.3 %	41.1	58.4	-17.3 %	37.1	54.9	-17.8 %
<35 weeks	17.4	27.5	-10.1 %	22.8	31.9	-9.1 %	21.3	30.7	-9.4 %
<32 weeks	10.5	25.0	-14.5 %	12.5	17.7	-5.2 %	11.9	19.6	-7.7 %

Source: Response to FDA Question 1, 10/6/06
[a] Four 17-HPC-treated patients were "lost-to-follow-up." They are counted as deliveries at their gestational ages at time of last contact (18.6, 22.0, 34.4 and 36.6 weeks).

The Applicant conducted several efficacy analyses with and without the University of Alabama site. The analyses included a center-by-treatment interaction analysis using logistic regression, evaluation of consistency of treatment effect across centers using the Breslow-Day statistic. The Applicant concluded that the treatment differences at < 32 weeks with (-7.7) and without (-5.2) the University of Alabama data, and the relative risks of birth < 32 weeks (0.68 with and .70 without the University of Alabama data) were statistically similar.

Medical Officer's Comment:

- *The apparent reduction in the < 32 week delivery rate at the University of Alabama compared to all other sites (-14.5% [Alabama] vs. -5.2% [other sites combined]) reflects both a lower delivery rate in 17-HPC subjects and a higher delivery rate in the vehicle subjects at < 32 weeks as compared to the other centers involved in the trial.*
- *However, the Applicant submitted several analyses that that supported their contention that the overall finding of a treatment benefit for 17-HPC at <320 weeks gestation was not driven by the effect at the Alabama site.*

The percent of Black subjects in Study 17P-CT-002 was 59% in both groups. 17-HPC, compared to vehicle, reduced the rate of preterm birth of <37 weeks gestation for both the Black (36.1% vs. 52.2%) and the Non-Black (38.6% vs. 58.7%) populations.

Medical Officer's Comments:

- *Although the percent reduction of PTB was comparable in both black and non-black subjects, the percent of black subjects (59%) in Study 17P-CT-002 was substantially*

greater than the percent of blacks in the general U.S. population (approximately 12%). Refer to the Clinical Team Leader Memo for a detailed description of the FDA statistician's analysis versus the Applicant's analysis of the potential influence of race on the efficacy results.

Efficacy Summary:
In a single adequate and well controlled trial (Study 17P-CT-002), treatment with 17-HPC, compared to treatment with vehicle, reduced the percentage of women with a preterm birth $< 37^0$ weeks gestation from 54.9% (vehicle group) to 37.1% (17-HPC group). The effect of 17-HPC treatment in reducing preterm births $< 37^0$ weeks gestation was sufficiently persuasive ($p < 0.001$) to meet the level of statistical significance generally expected to support approval of a new drug product based on the findings of a single trial. The proportions of women delivering at $< 35^0$ and $< 32^0$ weeks also were lower among women treated with 17-HPC compared to those treated with vehicle. These latter changes, although statistically significant, did not meet the level of statistical significance generally expected to support approval of a drug product based on the findings from a single clinical trial.

Additional endpoints evaluated neonatal outcomes, including the proportions of infants with birth weight of < 2,500 and < 1,500 g. There was a statistically significant decrease in infants < 2,500 g in the 17-HPC group (27% HPC group vs. 41% vehicle group). The trend toward a lower proportion of < 1,500 g infants (8.6% in the 17-HPC group vs. 13.9% in the vehicle group), however, was not statistically significant. Mean birth weight was numerically higher in the 17-HPC group, but the difference was not statistically significant.

Medical Officer's Comments:
The major strengths of the original application were:

- *There was a statistically significant reduction in preterm births at < 37, <35, and <32 weeks gestation. The reduction at <37 weeks was statistically convincing ($p<0.001$) and sufficient to support approval based on the findings from a single study.*
- *The proportion of infants with a birthweight < 2500 g, corresponding approximately to < 37 weeks gestational age, was statistically significantly lower in the 17-HPC arm than in the vehicle arm.*
- *The prolongation of pregnancy, defined as the time from randomization to delivery or date last pregnant, was numerically longer, by a mean of six days, in the 17-HPC group compared to the vehicle group. While this is not statistically significant, this prolongation is clinically important.*

The major weaknesses of the original application were:

- *It relied on a single multicenter study for evidence of effectiveness.*
- *There was no statistically significant improvement in neonatal mortality or morbidity.*
- *There was a possible imbalance in the weighted contribution of the centers, which may have affected the results at <32 weeks*

Safety

Study 17P-CT-002.

Maternal Deaths and Serious Adverse Events

There were no maternal deaths in Study 17P-CT-002. There were 3 reports of a serious adverse event (SAE) in the mothers, all in the 17-HPC group; none were thought by the investigators to be related to the study drug. The SAEs were: one case of a pulmonary embolus 8 days after delivery; one case of cellulitis at the study medication site; and one case that included postpartum hemorrhage, respiratory distress, and endometritis.

Discontinuations Secondary to Adverse Events

In Study 17P-CT-002, 7 (2.2%) of the 17-HPC-treated subjects discontinued therapy prematurely due to adverse events, compared to 4 (2.6%) of vehicle-treated subjects. In the 17-HPC-treatment group, the adverse events and the numbers of subjects reporting them were urticaria (n=3), injection site pain or swelling (n=2), arthralgia (n=1), and weight gain (n=1). In the vehicle-treatment groups, the adverse events and the numbers of subjects reporting them were pruritus (n=2), urticaria (n=1), and injection site pain (n=1).

Miscarriages, Stillbirths and Neonatal Deaths

The only safety finding of significant concern was an apparent increase in early pregnancy losses in the 17-HPC-treated subjects. The numbers of miscarriages, stillbirths and neonatal deaths in the treatment and vehicle groups are summarized in Table 7. There was a trend toward an increase in the second trimester miscarriage rate (pregnancy losses prior to 20 weeks of gestation) and a suggestion of a possible increase in the proportion of stillbirths (death of a fetus prior to or during delivery) in the 17-HPC-treatment group. Conversely, the incidence of neonatal deaths was numerically reduced by slightly more than 50% in the 17-HPC group (2.6% vs. 5.9%), although the difference was not statistically significant. The overall incidence of combined fetal and neonatal mortality from the onset of treatment to delivery was similar in the 2 treatment groups (19 of 306 [6.2%] in the 17-HPC group and 11 of 153 [7.2%] in the vehicle group).

Table 7 Miscarriages, Stillbirths, and Neonatal Deaths

Pregnancy Outcome	17-HPC N=306 n (%)	Placebo N=153 n (%)	Nominal P-value [A]
Miscarriages <20 weeks gestation	5 (1.6)	0	0.1746
Stillbirth	6 (2.0)	2 (1.3)	0.7245
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.1159
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.6887**

[A] No adjustment for multiple comparisons.

Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

Medical Officer's Comments:

- *The observed reduction in neonatal deaths was offset by an increase in second trimester miscarriages and stillbirths in the 17-HPC group. Thus, when considering overall mortality, there was no net survival benefit.*
- *A similar trend toward an increase in the rates of miscarriage and possibly stillbirth was not observed in the 17-HPC-treatment group in the smaller supportive Study 17P-IF-001.*
- *These findings were presented to the Advisory Committee for Reproductive Health Drugs in 2006. The recommendation of the majority of the members was that this observation required further investigation, but that the investigation could be conducted post-approval.*
- *Other studies in which 17-HPC has been investigated to prevent preterm birth, which for the most part have been published subsequent to the original review of NDA 021945, have had differing findings (i.e., numeric increases or decreases) in the proportion of early pregnancy losses in women treated with 17-HPC relative to the control group. Most of these studies have been conducted in other populations (e.g., women at risk of preterm birth because of twin or triplet pregnancy or because of a short cervix). See section 7.7.2 for a review of these studies.*

Common Adverse Reactions

The most common serious adverse events (SAEs) were congenital anomalies. The number and type of these anomalies appeared evenly distributed over the two treatment arms: 17-HPC group – 2.2%, 9/404; Placebo group – 1.9%, 4/209. The rate of congenital anomalies in this study did not differ from the background rate at birth in the U.S. population (2-3% of births).

The most common adverse events (> 5% incidence) and the percent of subjects reporting them in the *17-HPC group* were injection site pain (34.8%), injection site swelling (17.1%), urticaria (12.3%), pruritus (7.7%), injection site pruritus (5.8%), nausea (5.8%), and contusion (5.5%). The most common adverse events (and the percent of subjects reporting them) in the *vehicle group* were injection site pain (32.7%), urticaria (11.1%), contusion (9.2%), injection site swelling (7.8%), pruritus (5.9%), and neonatal death (5.9%).

Selected Pregnancy Complications

Of nine complications of pregnancy reported by the Applicant (in both the principal Study 17P-CT-002 and the initial formulation Study 17P-IF-001), this reviewer identified three where the percentage of affected subjects was numerically greater in the 17-HPC arm. The pregnancy complications were gestational diabetes, oligohydramnios, and preeclampsia (see Table 8).

Table 8 Selected Pregnancy Complications

Pregnancy Complication	Study	17-HPC N (%)	Vehicle N (%)
Gestational Diabetes	CT- 002	17 (5.6)	7 (4.6)
	IF- 001	8 (8.6)	0 (0.0)
Oligohydramnios	CT- 002	11 (3.6)	2 (1.3)
	IF- 001	2 (2.2)	1 (1.9)
Preeclampsia	CT- 002	27 (8.8)	7 (4.6)
	IF- 001	6 (6.5)	2 (3.8)

Source: Table 12-3 Final Report for Study 17-CT-002 and Study 17-IF 001

Brief Summary of Safety Findings from Study 17P-IF-001:
There was no increase in the incidence of miscarriage or stillbirth rate in the 17-HPC treated subjects. There was only one case of miscarriage in each treatment arm. In terms of stillbirths, there were two cases in the vehicle arm compared to one case in the 17-HPC arm. There were two neonatal deaths in the 17-HPC arm, and none in the vehicle arm. The percentages of subjects with gestational diabetes and preeclampsia were higher in the 17-HPC treated subjects.

Follow-up Safety Study (Study 17P-FU):
This was a safety study of children whose mothers had participated in Study 17P-CT-002 (Northen 2007[15]). The study collected data with a validated child development instrument (the Ages and Stages Questionnaire [ASQ]), a survey questionnaire concerning the health and development of the child, and a physical examination.

All children were at least two years of age at the time of the follow-up assessments. The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received 17-HPC compared with vehicle in Study 17P-CT-002. Two hundred seventy-eight (278) children were enrolled: 194 from the 17-HPC arm, and 84 from the vehicle arm of Study 17P-CT-002.

There was no difference between the 17-HPC and vehicle groups in the percentage of children who scored below the cutoff for at least one developmental area of the primary endpoint of the ASQ. The percentages of children who scored below the ASQ cutoff in each of the five individual developmental areas were similar in the 17-HPC and vehicle groups. Developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age-mates in physical, mental, social/emotional, or speech development, was reported for a comparable percentage in the 17-HPC and vehicle groups. The percentages of children with delay in specific developmental areas, based on both the ASQ and an independent diagnosis of developmental delay by a professional, also were similar (see Table 9).

Table 9 Development Delay in Children from Study 17P-CT-002 *

ASQ Area of Development below Cutoff	17OHP-C n = 13 (6.7%)	Vehicle n = 8 (9.8%)
	Percent Affected	
Communication	4.7	8.5
Gross motor	1.6	2.4
Fine motor	5.2	3.6
Problem solving	2.6	6.1
Personal-social	2.6	1.2

* Includes only children who had an ASQ score compatible with a developmental delay and an independent diagnosis of developmental delay by a professional.
Source: Final Study Report: Study 17P-FU

Medical Officer's Comments:

- *There were no signals of increased rates of developmental delay in offspring of 17-HPC-treated women in the follow-up study of children.*
- *The ASQ was completed for 275 children, 193 from the 17-HPC group and 82 from the vehicle group (almost 80% of offspring).*
- *The age of the children at the time of completion of the ASQ ranged from 30 to 64 months; mean age at time of completion did not differ between the 17-HPC and vehicle groups (47.2 vs. 48.0 months).*

Safety Conclusions:

- *There are no definitive safety issues that have been identified.*
- *There was a suggestion of an increase in miscarriages and stillbirths in 17-HP- treated subjects, the most concerning safety signal.*
- *There was also a suggestion that 17-HPC may impair maternal glucose tolerance, requiring further study; there is reason to study further the effects of 17-HPC on amniotic fluid levels and preeclampsia.*
- *Injection site pain, swelling and pruritus were the most common adverse events (AEs) and reasons for discontinuation.*
- *There were no signals of increased rates of developmental delay in the limited follow-up study of children; however, this study was an addition to the principal study and as such, had some deficiencies; e.g., less than complete recruitment into the study and lack of neurologic examination in children who screened positive.*

2.5.4 Advisory Committee (August 29, 2006)

A meeting of the Advisory Committee for Reproductive Health Drugs (ACRHD) was held in August 2006 to review data submitted in the NDA for the use of 17-HPC for the prevention of recurrent preterm birth. Refer to the primary Medical Officer's review in the first cycle (Oct. 18,2006) for a more detailed summary of this meeting.

The major issues that the FDA asked the ACRHD to consider included: adequacy of the clinical data to support the effectiveness of 17-HPC; any potential safety signals; the adequacy of safety data; and the potential need for post-approval clinical study(ies).

The committee thought that the endpoints of preterm birth at 35 and 32 weeks were adequate surrogate endpoints for infant/childhood morbidity/mortality. The committee generally believed that data from Study 17P-CT-002 demonstrated substantial evidence that 17-HPC prevents preterm birth prior to 35 weeks gestational age but not at < 32 weeks gestational age; however, the committee did not have the correct statistical results for < 32 weeks gestational age. (Upon recalculation, the result presented to the committee, that the endpoint of < 32 weeks was not statistically significant, was subsequently found to be statistically significant.) The committee unanimously thought further study was needed to evaluate the potential association of 17-HPC with increased risk of second trimester miscarriage and stillbirth, but most believed that this could be done post approval.

The Advisory Committee made multiple recommendations for further studies which are summarized in the following bullets:

- Further assessment of efficacy and safety post approval
- Specific studies to evaluate the potential connection between 17-HPC and miscarriages/stillbirths
- Long term follow-up studies (possibly a registry) of children exposed to 17-HPC, including evaluation of reproductive health/genital development, fertility, and carcinogenic potential
- Evaluation of potential maternal complications such as depression, and gestational diabetes
- Elucidation of the pharmacokinetic and pharmacodynamic properties of 17-HPC

Medical Officer's Comments:

- *The* ACRHD *recommendations would support approval under the Subpart H regulations because initial approval would be based on a surrogate for infant morbidity and mortality (i.e., reduced preterm births at <37 weeks).*
- *Long term follow-up studies (possibly a registry) of children exposed to 17-HPC, including evaluation of reproductive health/genital development, fertility, and carcinogenic potential was recommended by ACRHD because of non-reassuring result concerning fertility and reproductive performance in rodents in a publication by Pushpalatha (2005[16]); however, these animal studies were not conducted according to FDA standards. Subsequently, upon the recommendation of the Division, the applicant conducted a GLP-compliant reproductive toxicology study, and the results of that study were reassuring (see Section 4.3). Because of this new data, the Division decided not to require the registry or similar studies at the present time. This decision will be revisited if the data from the infant follow-up study (17P-FU-004) raises concern in the future.*

- *There was strong consensus that" required post-marketing studies" should be conducted, particularly to further assess if there is an increase in second trimester miscarriage and stillbirths.*
- *At the time of the Advisory Committee meeting, the general consensus was that the greatest impact on neonatal morbidity and mortality was attributable to early preterm birth, e.g., births at < 35 weeks and < 32 weeks of gestation. Since that time, multiple studies evaluating the consequences of "late preterm birth" (34-36^{6} weeks gestation) and even early term birth (37$^{0/7}$ – 38$^{6/7}$ weeks gestation) have been published since this advisory committee meeting. Overall, these studies demonstrate that there is greater morbidity than previously thought in these offspring. Increased neonatal morbidities include respiratory, metabolic, infectious, and neurologic disease. Childhood morbidities include neurologic, cognitive and behavioral delays. Most of these data were not published yet at the time of this meeting. Selected publications are summarized below*:

2.5.5 Literature – Late Preterm Births

Review Articles

Martin et al, 2009[17]
This is a review of recent trends in late preterm births in the United States, published in the National Center for Health Statistics (NCHS) Data Brief (No. 24). The preterm (less than 37 weeks of gestation) birth rate rose by more than 20 percent in the United States between 1990 and 2006. Most of this increase was among infants born at 34 to 36 completed weeks of pregnancy, or during the period known as "late preterm." The authors state that "it is becoming increasingly recognized that infants born late preterm are less healthy than infants born later in pregnancy. Late preterm babies are more likely than term babies to suffer complications at birth such as respiratory distress, to require intensive and prolonged hospitalization; to incur higher medical costs; to die within the first year of life; and to suffer brain injury that can result in long-term neurodevelopmental problems. Accordingly, *increased high levels of late preterm births are an important public health issue."*

Adams-Chapman, 2006[18]
This author conducted a review of literature regarding the neurodevelopmental (ND) outcome of the late preterm infant. He concluded that there is "growing concern that the late preterm infant may be at significant risk for brain injury and adverse long term neurodevelopmental outcome. Multiple factors related to their developmental immaturity may mediate the risk for brain injury and subsequent abnormal neurologic sequelae, including the risk for development of intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), hypoxic respiratory failure, hyperbilirubinemia, and infection." He further states that "it is also important to recognize that the late preterm brain is only a fraction of the full-term brain weight and a *significant proportion of brain growth, development, and networking occurs during the last six*

weeks of gestation. These tissues are vulnerable to injury during this critical time period of development."

Studies

The Consortium on Safe Labor, 2010[19]
The authors assessed *short-term respiratory morbidity* in late preterm births compared with term births in a cohort of deliveries in the United States. They retrospectively collected electronic data from 12 institutions (19 hospitals) across the United States on 233,844 deliveries between 2002 and 2008. Charts were abstracted for all neonates with respiratory compromise admitted to a neonatal intensive care unit (NICU), and late preterm births were compared with term births in regard to resuscitation, respiratory support, and respiratory diagnoses. "Of 19,334 late preterm births, 7,055 (36.5%) were admitted to an NICU and 2,032 had respiratory compromise. Of 165,993 term infants, 11,980 (7.2%) were admitted to an NICU, 1,874 with respiratory morbidity."

McIntire et al, 2008[20]
The objective of this study was to analyze *neonatal mortality and morbidity rates* at 34, 35, and 36, weeks of gestation compared with births at 39 weeks. The authors conducted a retrospective cohort study of neonates delivered to women who received prenatal care over the past 18 years at the University of Texas Southwestern Medical Center, Dallas, Texas. Late preterm singleton live births constituted approximately 9% (n=21,771) of all deliveries at their hospital and accounted for 76% of all preterm births. "Late preterm neonatal mortality rates per 1,000 live births were 1.1, 1.5, and 0.5 at 34, 35, and 36 weeks, respectively, compared with 0.2 at 39 weeks ($p < 0.001$). Neonatal morbidity was significantly increased at 34, 35, and 36 weeks, including ventilator-treated respiratory distress, transient tachypnea, grades 1 or 2 intraventricular hemorrhage, sepsis work-ups, culture proven sepsis, phototherapy, for hyperbilirubinemia, and intubation in the delivery room."

Tomashek et al, 2007[21]
The objective of this study was to assess differences in *mortality* between late-preterm (34-36 weeks) and term (37-41 weeks) infants. The authors used US period-linked birth/infant death files for 1995 to 2002 to compare overall and cause-specific early-neonatal, late-neonatal, post-neonatal, and infant mortality rates between singleton late-preterm infants and term infants. "Infant mortality rates in 2002 were 3 times higher in late-preterm infants than term infants (7.9 versus 2.4 deaths per 1000 live births); early, late, and post-neonatal rates were 6, 3, and 2 times higher, respectively. During infancy, late-preterm infants were approximately 4 times more likely than term infants to die of congenital malformations (leading cause), newborn bacterial sepsis, and complications of the placenta, cord, and membranes. Early-neonatal cause-specific mortality rates were most disparate, especially deaths caused by atelectasis, maternal complications of pregnancy, and congenital malformations." The authors were able to conclude that *late-preterm infants have higher mortality rates than term infants throughout infancy*.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Three study sites were inspected by the Division of Scientific Investigation (DSI) after the initial submission of this NDA. There were no concerns regarding the quality and integrity of the data that was submitted in the original review. Final reports were received during the previous review cycle, and there were no violations that would impair the acceptability of the clinical data.

3.1.1 Institutional Review/Ethics/Consent Form:

Prior to starting the confirmatory studies (17-ES-003; 17-FU-004), the protocol, informed consent, advertisements (to be used for subject recruitment), and any other written information regarding this study will be provided to the subject or the subject's legal guardian and will be approved by the IRB/IEC.

A written informed consent, in compliance with Part 50 of Title 21 of the Code of Federal Regulations (CFR), shall be obtained from each subject/legal guardian prior to entering the study or performing any unusual or non-routine procedure that involves risk to the subject. Women who are not fluent in English will be enrolled by a person fluent in their language and both verbal and written informed consent obtained in that language; if such are not available, they will not be included.

3.2 Compliance with Good Clinical Practices

The investigator agrees that the studies will be conducted according to the principles of the ICH E6 Guideline on GCP and the principles of the World Medical Association Declaration of Helsinki. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

Data Handling/Quality Assurance
All aspects of the studies will be carefully monitored, by the Applicant or its designee, for compliance with applicable government regulations with respect to current GCP and current standard operating procedures.

The monitor will visit the investigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

Investigators and institutions involved in the study will permit trial-related monitoring, audits, (IRB/IEC) review, and regulatory inspection(s) by providing direct access to all study records. In

the event of an audit, the investigator agrees to allow the Applicant, representatives of the Applicant, the FDA, or other regulatory agency access to all study records.

3.3 Financial Disclosures

Investigators will be required to provide financial disclosure information to allow the Applicant to submit the complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR. In addition, the investigator must provide to the Applicant a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

In the Approvable Letter of October 20, 2006, 3 CMC deficiencies were listed. These deficiencies concerned (1) failure to detect photo-degradation products by the Applicant's HPLC method, (2) failure to demonstrate that the secondary packaging provided adequate light protection for the drug product, and (3) lack of adequate data to support a product expiration date of 24 months. In her review of first Complete Response, the primary Chemistry Reviewer, Donna Christner PhD, stated that the 3 deficiencies were adequately addressed, and she recommended Approval from a CMC perspective.

On Nov. 22, 2010 this chemistry reviewer made the following conclusions:

> *"This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for APPROVAL".*
>
> *The formulation in the phase 3 clinical trial is the same as the proposed commercial formulation. The Applicant provided comparability data between the commercial manufacturer and the 2 manufacturers of the clinical lots and they were found acceptable. Based on the submitted data, an expiration dating period of 24 months is granted when stored at controlled room temperature. In addition, the contents must be protected from light and stored in the upright position.*
>
> *Because the last facility recommendation was made over 2 years ago, inspections were requested for all facilities involved in the manufacture of the drug substance and drug product. A final overall ACCEPTABLE recommendation was made by the Office of Compliance on 26-Oct-2010.*

4.2 Clinical Microbiology

No new microbiology data were provided in the current submission. The microbiological stability of the product once the product (sterile vial) is penetrated was reviewed during the prior review cycle. The microbiology reviewer, James McVey PhD, concluded in his review signed on December 12, 2008, that the microbiology data provided by the Applicant were adequate to support an in-use shelf-life of 5 weeks once the vial stopper was penetrated in actual use.

4.3 Preclinical Pharmacology/Toxicology

The Approvable Letter of October 20, 2006, listed "a lack of nonclinical data from a multi-generational reproductive toxicology study" as a deficiency that would need to be resolved prior to approval of 17-HPC for the proposed indication. A submission to the NDA, received on June 16, 2008, contained the final Report for a multigenerational study in rats in which offspring exposed *in utero* were evaluated for potential effects on development, learning, and behavior. The study was conducted under Good Laboratory Procedures and was also audited by FDA inspectors. The study did not find any potential adverse effects on neurologic or reproductive development of offspring exposed to 17-HPC *in utero*.

On Nov. 24, 2010, the pharmacology/toxicology reviewer made the following recommendation: "The label for 17-alpha hydroxyprogesterone caproate for the prevention of recurrent preterm birth is satisfactory from the standpoint of pharm/tox."

His executive summary during the previous review cycle made the following points:

A. Brief overview of nonclinical findings: "A multi-generational reproduction study in rats did not show any adverse effects of Gestiva on the health of the dams, fetuses, offspring, or second generation offspring."

B. Pharmacologic activity: "17α-HPC was shown to help maintain pregnancy in pregnant rabbits but not in the pregnant rat, mare or squirrel monkey. It is not clear how 17α-HPC exerts its effects on the uterus to prolong gestation but the mechanism does not seem to stem from direct uterine relaxation."

4.4 Clinical Pharmacology

In consultation with the clinical pharmacologist, the following phase 4 postmarketing commitments were agreed upon by both the Division and Hologic in the second review cycle:

1. "The Applicant will provide data characterizing the pharmacokinetics (PK) of 17 α-hydroxyprogesterone caproate (17-HPC) and its metabolites in plasma and urine in pregnant women at several periods throughout the pregnancy.

2. The Applicant will conduct an *in vitro* study in human hepatocytes to determine whether hydroxyprogesterone caproate induces or alters the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.

There were 2 new literature reports on the in vitro and preclinical metabolism of 17-HPC since the original NDA review. The new data were consistent with and support previous findings that 17-HPC can be metabolized but *the caproate ester bond appears to remain intact*.

NIH – Obstetric Pharmacology Study
A study evaluating the pharmacology of 17-HPC in pregnant women with a previous history of preterm birth (ClinicalTrials.gov identifier: NCT00409825) was conducted by the University of Pittsburgh and NIH (Principal Investigator: Steve Caritis, M.D.). Hologic has spoken with Dr. Caritis regarding the status of the study. Hologic proposes to provide to the Division the data from this study (contingent upon release by Dr. Caritis subsequent to publication in a peer review journal).

Because of the comprehensive scope and size of the Caritis/NIH 17-HPC PK study and the invasive nature of conducting such a study, particularly in pregnant women, Hologic believes it is not necessary or appropriate to duplicate this study. Provided that the results of the Caritis/NIH study are sufficient to characterize the PK of 17-HPC and its metabolites, Hologic would anticipate conducting no further research in this area.

17-HPC exposure-response relationship and the effect of body weight on the PK of 17-HPC
Hologic proposes to use a population pharmacokinetic/pharmacodynamic (PK/PD) approach to explore the exposure-response relationship and the effect of BMI on the PK of 17-HPC.

Approximately 450 subjects will participate in the population PK sub-study of Study 17-ES-003. Subjects in the PK population will be stratified based on BMI (≤ 28 and > 28), such that approximately 40% and 60% of subjects are in each BMI category, respectively. This sample size, while not based on any statistical considerations, will enable generation of a sparse sample that will permit adequate nonlinear modeling of the PK/PD effects of 17-HPC.

Effect on 17-HPC PK of concomitant medications (strong inducers or inhibitors of drug metabolizing enzymes)
Concomitant medication information will be collected throughout the efficacy and safety study and will also be address in the hepatocyte study. Effects of known strong inducers or inhibitors of metabolizing enzymes on PK of 17-HPC will be examined by including them as covariates in the population PK model, if feasible.

Medical Officer's Comment:

- *This reviewer, in consultation with the clinical pharmacology reviewer, agrees with these proposals.*

5 Sources of Clinical Data

This information is described in the primary medical officer's review during the original review cycle (See primary Medical Officer Review signed 10/19/2006).

6 Review of Efficacy

A summary review of the efficacy data submitted for approval is located in Sections 1.2 and 2.5.1 of this review.

The protocol for the confirmatory clinical trial (Study 17P-ES-003) required as a component of approval under Subpart H is discussed below. Although the protocol was reviewed and found acceptable by the Division in 2009, further review was undertaken in the current review cycle, and additional revisions have been requested. The Applicant has agreed to make these revisions, and a revised protocol will be submitted in March 2011, as part of the PMR for this Confirmatory trial.

Study 17P-ES-003

6.1 Indication

17-HPC is indicated for the reduction of risk of preterm birth in pregnant women with a history of at least one spontaneous preterm birth.

6.1.1 Methods

This study is a multicenter, randomized, double-blind, placebo-controlled clinical trial in women with a singleton pregnancy, aged 16 years or older, with a history of a previous singleton spontaneous preterm delivery. The protocol for this study was submitted to the Division for review and found to be acceptable prior to beginning the study.

6.1.2 Primary Endpoint(s)

Primary Efficacy Endpoints

There are two co-primary efficacy endpoints:

- Preterm birth prior to 35^0 weeks of gestation (as determined by project gestational age). All deliveries occurring from randomization until 35^0 weeks of gestation, including miscarriages occurring from 16^0 through 19^0 weeks of gestation and elective abortions, will be included.

- Composite neonatal morbidity and mortality index. The composite index includes neonatal mortality and the following morbidity components occurring in liveborn infants at any time during the birth hospitalization up through discharge from the NICU or the first 28 days of life (See Section 13.2 for definitions):
    - Grade 3 or 4 Intraventricular Hemorrhage (IVH)
    - Respiratory Distress Syndrome (RDS)
    - Bronchopulmonary Dysplasia (BPD)
    - Necrotizing Enterocolitis (NEC)
    - Proven sepsis

Medical Officer's Comment:

- *As requested by the Division, the Applicant agreed that all sites (U.S. and non-U.S.) will use the same pre-defined definitions of neonatal morbidities; these definitions were included in the final protocol and are acceptable to this reviewer.*

6.1.3 Secondary Endpoints(s)

Secondary Outcomes

The key secondary outcome of this study is to:

- Exclude a doubling of the risk in the 17-HPC group compared to the placebo group of the composite of:
    - fetal/early infant death, defined as
        - spontaneous abortion/miscarriage (delivery from 16^0 through 19^6 weeks of gestation) or
        - death (from minutes after birth until 28 days of life) occurring in liveborns born at less than 24 weeks gestation.
    - stillbirth (antepartum or intrapartum death from 20 weeks gestation through term), in the 17-HPC group compared to the placebo group.

Other secondary outcomes:

- Preterm birth < 32^0 weeks of gestation.
- Preterm birth < 37^0 weeks of gestation.
- Dose-plasma concentration-time data of 17-HPC analyzed using a nonlinear mixed effects modeling (NONMEM) of a population approach. The dependence of apparent clearances and volumes on BMI examined as the primary covariate through its formal inclusion in the NONMEM models.
- Pharmacokinetic models to evaluate effects on concomitant medications that may affect the inhibition or induction of 17-HPC will be evaluated and modeled as data permit.

6.1.4 Other Endpoints

Additional outcomes that will be measured include:

- Spontaneous delivery, defined as following premature rupture of membranes (pPROM) from $20^0 – 37^0$ or spontaneous labor from 20^0 - 35^0 weeks of gestation, respectively, or miscarriage from 16^0 through 19^6 weeks of gestation.
- Indicated preterm birth (generally medically/surgically induced delivery for medical/surgical indications) prior to 37^0 weeks of gestation. Elective abortions will be defined as indicated preterm births.
- Gestational age at delivery.
- Miscarriage (delivery from 16^0 through 19^6 weeks of gestation).

Additional neonatal outcomes that will be measured are listed below.

- The following *individual components* of the composite mortality/morbidity index:
    - IVH
    - RDS
    - BPD
    - NEC
    - Proven sepsis
- Birth weight
- Seizures
- Retinopathy of prematurity (ROP)
- Patent ductus arteriosus (PDA)
- Infant hospital days: Time from birth to hospital discharge
- Number of days of neonatal respiratory therapy: Defined as the number of days on ventilator support and/or oxygen therapy
- Transient tachypnea
- Persistent pulmonary hypertension

Medical Officer's Comment:

- *The Division provided advice to the Applicant on January 5, 2011. On January 7, the Applicant agreed to the following:*
    - *Change in the primary endpoint: "Based on comments received from the Division during the above referenced teleconference, the Applicant hereby commits to modify Protocol 17P-ES-003 such that* ***delivery < 35 weeks and the composite neonatal index endpoints will be co-primary endpoints.****"*

6.1.5 Study Design

Type of Study:
A Phase 4, Multi-Center, Randomized, Double-Blind Study of 17 α-Hydroxyprogesterone Caproate (17-HPC) versus Placebo for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous Preterm Delivery.

Drug Product
17-HPC will be supplied as 5 mL of a sterile solution in a multiple dose glass vial. Each mL will contain 17α-hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), castor oil (28.6% v/v), benzyl benzoate (46% v/v), and benzyl alcohol (2% v/v) as preservative.

Vehicle – 5 mL multidose vials containing are identical in color and appearance to 17-HPC and have the same excipient ingredients as 17-HPC, but do not have the active compound.

Dosing Regimen
17-HPC is to be administered intramuscularly at a dose of 250 mg (1 mL) once each week beginning at 16^0 weeks to 20^6 weeks of gestation until Week 37 of gestation or delivery.

Overall Study Plan
The proposed study is a multi-center, randomized, double-blind, vehicle-controlled clinical trial in women with a singleton pregnancy, aged 16 years or older, with a history of a previous singleton spontaneous preterm delivery. A total of 1707 subjects will be randomized in a 2:1 ratio (1138 in the active arm and 569 in the placebo arm) to receive either 17-HPC or placebo, respectively. Subjects will receive weekly injections of study drug from randomization (16^0 through 20^6 weeks of gestation) until 36^6 weeks of gestation or delivery, whichever occurs first. PK assessments will be made based on a sparse sampling of approximately 450 subjects (300 active and 150 placebo), stratified according to BMI to analyze the dose-plasma concentration-time relationship of 17-HPC. Randomized subjects will be followed up to 30 ± 7 days after the last dose of study drug or discharge from the delivery hospitalization, whichever occurs later. Neonates of randomized subjects will be followed until at least 28 days of life. Neonates who remain hospitalized at 28 days will be followed until discharge from the birth hospitalization or 120 days after birth, whichever occurs first.

Subjects/Populations
Approximately 1707 subjects will be enrolled and randomized at multiple sites both in the US and at sites outside the U.S. A subject is considered enrolled in the study if she receives the initial "trial (vehicle only) injection." The trial injection is used as a test for compliance prior to randomization.

Inclusion Criteria

1. Age ≥ 16 years.
2. Singleton gestation.
3. Gestational age $\geq 16^0$ weeks of gestation and $\leq 20^6$ weeks of gestation at the time of randomization, based on clinical information and evaluation of the first ultrasound.
4. Documented history of a previous singleton spontaneous preterm delivery. Spontaneous preterm birth is defined as delivery from 20^0 to 36^6 weeks of gestation following spontaneous preterm labor or pPROM. Where possible, the gestational age of the previous preterm birth (referred to as the qualifying delivery) should be determined. If the gestational age

at delivery is obtained directly from the medical record and more than one gestational age appears, the latest will be used. As a validation of the gestational age of the previous delivery, if the infant weighed more than 3300 grams (the birth weight 90th percentile for 36 weeks gestational age), this will not qualify as preterm. The previous preterm delivery cannot be an antepartum stillbirth.

Exclusion Criteria

1. Multifetal gestation.
2. Known major fetal anomaly or fetal demise. An ultrasound examination must be performed between 14^0 through 20^3 weeks of gestation to rule out fetal anomalies.
3. Progesterone treatment in any form (e.g., vaginal, oral, intramuscular) during the current pregnancy.
4. Heparin therapy during the current pregnancy or a history of thromboembolic disease.
5. Maternal medical/obstetrical complications including:
    - Current or planned cerclage
    - Hypertension requiring medication
    - Seizure disorder
6. Subjects with a uterine anomaly (uterine didelphus or bicornuate uterus). However, subjects with uterine fibroids are eligible for the trial.
7. Unwillingness to comply with and complete the study.
8. An ultrasound at 14^0 through 20^3 weeks of gestation cannot be arranged before randomization.
9. Participation in an antenatal study in which the clinical status or intervention may influence gestational age at delivery.
10. Participation in this trial in a previous pregnancy. Women who were screened in a previous pregnancy, but not randomized, do not have to be excluded.

Medical Officer's Comments:

- *The inclusion/exclusion criteria are acceptable.*
- *Allowing adolescents who are ≥ 16 years old to enroll will help to provide data in the adolescent population.*

Procedures/Daily Visits

Each subject will be seen for weekly study visits to administer intramuscular injections of study drug. The weekly visits will occur until the subject is 36^6 weeks of gestation or delivery, whichever occurs first. Three blood samples will be collected from approximately 450 subjects (300 in the active arm and 150 in the placebo arm) for the population PK analysis at specified visits during the trial. If the treatment is interrupted for any reason, the subject will be encouraged to resume treatment with the study drug and continue until 36^6 weeks of gestation or delivery, whichever occurs first.

At each study visit, the subject will be asked about possible adverse events (AE[s]) experienced since the last injection, the use of concomitant medications, and information related to additional risk factors for miscarriage will be collected.

The subject's ability to comply with the study protocol and procedures will be assessed at the Initial Evaluation (Visit 2). The subject will receive an injection (referred to as the trial injection) of the placebo (1 mL inert oil). The subject will be told that this injection does not contain the active drug but is a test for compliance with the treatment regimen and for any unusual reactions to the injection. She will be asked to return within one week for randomization. Subjects may return any time from three to seven days after the trial injection, as long as randomization occurs from 16^0 through 20^6 weeks of gestation.

Overall subject compliance with study treatment will be assessed by determining the number of injections received. The date of each injection will be recorded in the subject's case report form (CRF). All enrolled subjects will be followed until the End of Study Visit, 30 ± 7 days after the last dose of study drug or delivery, whichever occurs later. The primary outcome measure and secondary maternal outcome measures will be determined based on the date of delivery and the estimated date of confinement (EDC), which is evaluated in a standardized manner. Neonates of randomized subjects will be followed until discharge from the birth hospitalization or 120 days after birth, whichever occurs first. The secondary neonatal outcome measures will be determined from review of the neonatal medical record and will be based on standardized definitions of the morbidity measures.

PK assessments will be made based on a sparse sampling of approximately 450 subjects (300 active and 150 placebo) stratified according to BMI (≤ 28 and > 28) to analyze the dose-plasma concentration-time relationship of 17-HPC. Three blood samples will be drawn:

1. Before study drug dosing at either Visit 7 or 8 (i.e., Dose 5 or 6).
2. Before study drug dosing at either Visit 9 or 10 (i.e., Dose 7 or 8).
3. At a separate, non-dosing visit 1 to 6 days after Visit 10, 11, or 12 (i.e., one to six days after Doses 8, 9, or 10). subjects will be stratified 2:1 (17-HPC: placebo) such than an even distribution of samples will be drawn on day 1, day 2, day 3, day 4, or day 5/6 post-dose. This will result in approximately 60 17-HPC and 30 placebo samples on each day.

The BMI-dependence of apparent clearance and volumes of distribution will be examined as the primary covariate. Pharmacokinetic models to evaluate effects on concomitant medications that may affect the inhibition or induction of 17-HPC will be evaluated and modeled as data permit.

A full schedule of assessments is provided in Table 10 below.

Table 10 Schedule of Events for the Study

Procedures	Baseline[a] Visit 1	Initial Evaluation[b] Visit 2	Active Treatment Period[c] Visits 3 to 36^6 Weeks of Gestation or Delivery	Delivery and Hospital-ization	Neonate Follow-up[d]	End of Study Visit[e]
Informed consent[f]	X					
Medical records release[g]	X					
Medical/obstetrical history	X					
Demographic information/social history	X					
Ultrasound (14^0 through 20^3)	X[h]					
Document previous preterm delivery	X					
Brief physical examination[i]	X					
Height	X					
Weight	X	X	X			
Prior medications[j]	X	X				
Concomitant medications[k]			X	X		X
Determine project gestational age and estimated date of confinement	X					
Schedule initial evaluation and randomization visit	X					
Trial injection		X				
Randomization[l]			X			
Collect blood sample for pharmacokinetic analysis			X[m]			
Study drug administration			X[n]			
Record adverse events (AEs)[o]		X[p]	X	X		X
Record pregnancy complications			X	X		
Record additional risk factors of miscarriage	X			X		
Maternal delivery information				X		
Neonatal information[q]				X	X	

[a] Visit will occur within 7 days before randomization.

[b] No later than 20^3 weeks of gestation and at least 3 days before randomization.

[c] Subject will report to the clinical site weekly for study drug administration until 36^6 weeks of gestation or delivery, whichever occurs first.

[d] The status of all neonates (alive or dead), regardless of when they are delivered and discharged from the hospital, will be obtained 28 days after delivery. If the neonate has been discharged from the birth hospitalization, the subject will be contacted by telephone 28 days after delivery to obtain the neonate's status.

[e] Should occur 30 ± 7 days after the last dose of study drug or 30 ± 7 days after delivery, whichever occurs later.

[f] To be completed before performing any baseline procedures.

[g] Must be signed by subject/legal guardian in order to obtain medical records of previous deliveries.

[h] If a 14^0 to 20^3 weeks of gestation ultrasound to rule out fetal anomalies has not been performed as part of standard prenatal care, one must be performed prior to randomization.

[i] A brief physical examination including a visual head-to-toe inspection of the subject's anterior and posterior torso and extremities.

[j] "Prior medications" includes all medications taken during pregnancy from the estimated date of confinement until study drug is randomly assigned.

[k] Concomitant medications must be recorded in the case report form through the End of Study Visit.

[l] Between 16^0 and 20^6 weeks of gestation.

[m] Three blood samples will be drawn from the PK population at the following times: (1) Before study drug dosing at either Visit 7 or 8 (i.e., dose 5 or 6). (2) Before dosing at either Visit 9 or 10 (i.e., Dose 7 or 8). (3) At a separate, non-dosing visit 1 to 6 days after Visit 10, 11, or 12 (i.e., 1 to 6 days after Doses 8, 9, or 10). Patients will be stratified 2:1 (17-HPC:placebo) such that an even distribution of samples will be drawn on day 1, day 2, day 3, day 4 or day 5/6 post-dose.

[n] Study drug will be administered weekly (once every 7 ± 2 days) from randomization (Visit 3) through 36^6 weeks of gestation or delivery, whichever occurs first.

[o] All subjects, regardless of when they deliver, should be contacted for an End of Study Visit to obtain AE information including medications to treat AE(s). The contact can be either in person or by telephone and should occur 30 ± 7 days after the last dose of study drug or 30 ± 7 days after delivery, whichever occurs later.

[p] AEs are recorded from administration of the trial injection through the End of Study Visit including medications to treat the AE. Preterm birth is an anticipated outcome and is not considered an AE.

[q] Neonates will be followed until at least 28 days of life. Neonates who remain hospitalized at 28 days will be followed until discharge from the birth hospitalization or 120 days after birth, whichever occurs first.

Source: Complete Response Study Report: 21,945

Restrictions

No attempt will be made to alter or mandate clinical management of the subjects. However, the *use of other prophylactic tocolytic drugs is discouraged*. If complications of the pregnancy arise, (for example, *need for a cervical cerclage* or detection of fetal anomaly/trisomy, or hospitalization for any reason including preterm labor) continuation of treatment will be at the discretion of the clinician managing the subject. These complications may not necessarily be indications for stopping treatment. Thus, if a subject is hospitalized, administration of the study drug should continue during hospitalization, if possible, as well as following discharge.

Medical Officer's Comment:

- *Women with a current or planned cerclage will be excluded; only unplanned cerclages will be allowed. The issue of allowing cerclage in these types of studies is controversial. This reviewer thinks the Applicant has provided a reasonable compromise.*

Subject Withdrawal/Lost to Follow-up

Subjects will be considered withdrawn from study drug if they are prematurely discontinued from administration of study drug (i.e., prior to the anticipated full course of study drug therapy for a reason other than delivery). The subject will remain on study and at a minimum, delivery data will be obtained. A subject will be considered withdrawn from the study if the subject delivery data are not obtained or if attempts to contact the subject for end of study assessments are unsuccessful. Randomized subjects who are withdrawn from the study will not be replaced.

Statistical Considerations:

Sample Size

In 3 studies of high-risk pregnant women, the rate of preterm birth < 35^0 weeks of gestation in women receiving vehicle ranged from 26.5% to 30%. The NICHD study also found that 17.2% of liveborn infants in women receiving vehicle had at least one event on the neonatal composite index. Using a 2:1 randomization, a total of 1665 live born infants are required to detect a

reduction of 35% in the rate of the composite index (from 17% to 11%) with a power of 90% (assuming a two-sided type I error of 5%). Assuming 2.5% of pregnancies will result in miscarriage or stillbirth, an additional 42 women need to be enrolled for a total of 1707 women (1138 active and 569 vehicle). A total sample size of 1707 subjects is also sufficient to detect a reduction of approximately 30% in the rate of preterm birth < 35^0 weeks of gestation (from 30% to 21%) using a two-sided type I error of 5% and power of 98%. The effect size for the neonatal composite index as well as preterm birth < 35^0 weeks gestation was chosen to represent a clinically significant reduction.

Since these outcome measures are co-primary outcomes, the power to detect significant differences between the treatment groups for *both* outcome measures may be reduced. If the outcome measures are independent, the power is 88.2% and if the outcome measures are perfectly correlated, the power is 90%. Data from the NICHD Study indicate these outcome measures are highly correlated, with 56% of liveborn infants of women who delivered < 35^0 weeks gestation having at least one event on the neonatal composite index compared with 2% of liveborn infants of women who delivered ≥ 35^0 weeks gestation. Thus, the power to detect significant differences between the treatment groups for *both* outcome measures is expected to be close to 90%.

There is also sufficient power to detect clinically significant reductions in the secondary outcomes of delivery < 32^0 and < 37^0 weeks of gestation as indicated in Table 11.

Table 11 Sample Size Calculation

Secondary Outcome	Outcome Rate in Vehicle Group	Percent Reduction	Power
Delivery < 32^0 weeks of gestation	20%	33%	92%
Delivery < 37^0 weeks of gestation	40%	33%	>99%

Source: Submission of Protocol: Study 17P-ES-003

Assuming a 4% fetal/early infant death rate, a sample size of 1707 subjects provides 82.8% power to rule-out a doubling in the risk of fetal/early infant death with a two-sided alpha of 5% (i.e., the upper bound of the confidence interval for the relative risk of 17-HPC compared to placebo will be ≤ 2.0). A fetal/early infant death rate of 4% is based on the results of Study 17P-CT-002.

Approximately 450 subjects will participate in the population PK sub-study. Subjects in the PK population will be stratified based on BMI (≤ 28 and > 28), such that approximately 40% and 60% of subjects are in each BMI category, respectively. Additionally, for the third blood sample draw, patients will be stratified 2:1 (17-HPC: placebo) such that an even distribution of samples will be drawn on day 1, day 2, day 3, day 4 or day 5/6 post-dose. This sample size, while not

based on any statistical considerations, will enable generation of a sparse sample that will permit adequate nonlinear modeling of the PK/PD effects of 17-HPC.
Five populations will be defined for analyses:

- Intent-to-treat (ITT) Population: ITT Population will consist of all randomized subjects. All subjects will be analyzed in the group to which they were randomized regardless of whether the subject received study drug.
- Modified ITT (MITT) Population: MITT Population will consist of all subjects in the ITT Population with outcome data of delivery date available.
- Per-Protocol (PP) Population: PP Population will consist of all subjects who are compliant with the study protocol. Each subject will be classified as compliant or not with the protocol based on the following criteria: subject was fully eligible (met all inclusion and had none of the exclusion criteria), at least 90% compliant with study drug, and outcome data available.
- Safety Population: The Safety Population will consist of all subjects who received any amount of study drug.
- PK Population: The PK Population will consist of subjects who received study drug and had PK data appropriate for analysis.

Inferential statistical analyses as specified will be conducted and all comparisons will be between the 17-HPC and placebo groups. An alpha level of 0.05 will be used for the primary and secondary analyses.

Primary Efficacy Analysis

The primary hypothesis for efficacy compares the proportion of subjects with a preterm delivery $< 35^0$ weeks of gestation between the 17-HPC (Π_{17P}) and vehicle (Π_V) treatment groups in the ITT Population and the percent of neonates with the neonatal composite index between the 17-HPC (P_{17P}) and vehicle (P_V) treatment groups in the Liveborn Neonatal Population. The null (H_O) and alternative (H_A) hypotheses are as follows:

H_O: $\Pi_{17P} = \Pi_V$ and $P_{17P} = P_V$

H_A: $\Pi_{17P} \neq \Pi_V$ or $P_{17P} \neq P_V$

An alpha level of 0.05 will be used for the primary analysis of both primary outcome measures as an adjustment for multiple comparisons is not required for testing the null hypothesis when stated as above.

Significant differences between the 17-HPC and vehicle group in the proportion of subjects who deliver prior to 35^0 weeks gestation will be determined using a Cochran-Mantel-Haenszel test stratified by gestational age at randomization (16^0 weeks - 17^6 weeks gestation and 18^0 weeks – 20^6 weeks gestation), where the effective sample sizes for each treatment group and stratum will be derived from a staggered entry Kaplan-Meier analysis using the time from randomization

until delivery as the analysis variable. Subjects with missing outcome data will be censored on the date last known pregnant.

The number and percentage of liveborn infants with the neonatal composite index will be presented by gestational age at randomization and overall, for each treatment group. Significant differences between the 17-HPC and vehicle group will be determined using the Cochran-Mantel- Haenszel procedure stratified by gestational age at randomization.

The percentage of subjects who deliver prior to 35^0 weeks of gestation will also be determined for subjects who received study drug (the Safety Population) and for the PP Population using the same analytic method as described above for the ITT Population.

If there are baseline imbalances between the treatment groups with respect to prognostic factors such as the number of previous preterm deliveries, an adjusted analysis of the primary outcome measures will be conducted using the Cochran-Mantel-Haenszel procedure (for the neonatal composite index) and/or a Cox regression model (for preterm delivery $<35^0$ weeks gestations). An additional analysis of the primary efficacy outcomes will be performed to determine if there is a treatment-by-site interaction. A Breslow-Day test for the neonatal composite index and/or treatment-by-site interaction terms will be included in a Cox regression model to determine if there is consistency of results across the sites.

Secondary Efficacy Analysis

Analyses of the secondary maternal outcomes (delivery $< 32^0$ and $< 37^0$ weeks of gestation) will be conducted using the ITT, Safety and PP populations. The number and percentages of subjects with delivery $< 32^0$ and $< 37^0$ weeks of gestation will be presented by treatment group and will be determined using the same analytic method as described above for the primary outcome. The number and percentage of subjects (MITT Population) and whose neonates died liveborn infants of subjects in the MITT Population) will also be presented by treatment group. Differences between treatment groups will be analyzed using the Cochran-Mantel-Haenszel test stratified by gestational age at randomization.

Medical Officer's Comments:

- *On January 3, the Division met with the Director of the Office of New Drugs to discuss the planned Approval Action for Makena under the Sub-part H regulation. Subsequently, all reviewing Medical Officers agreed to requesting the Applicant to change the original primary outcome to the co-primary outcome (including the neonatal mortality and morbidity index) as described above.*
- *Because the Data Safety Monitoring Board (DSMB) will not be reviewing efficacy data, no adjustment to the alpha level is required (see Section 7).*

Additional Analyses

The numbers and percentages of subjects with a spontaneous preterm birth prior to 37^0 and 35^0 weeks of gestation, and indicated preterm birth prior to 37^0 weeks of gestation, will be

determined and analyzed from a staggered Kaplan-Meier analysis as indicated above for the primary outcome. The number and percentages of subjects with a miscarriage and the numbers and percentages of neonates who had RDS, BPH, IVH, sepsis, NEC, ROP, PDA or seizures will be presented by treatment group. Differences between treatment groups will be analyzed using the Cochran-Mantel-Haenszel test stratified by gestational age at randomization.

Descriptive statistics of gestational age at delivery, birth weight, infant hospital days and days of neonatal respiratory therapy will be provided and the Wilcoxon Rank Sum test will be used to test for statistically significant differences between the 17-HPC and placebo groups.

Medical Officer's Comments:

- *The protocol has been revised by the Applicant to my satisfaction and therefore, I find it acceptable.*

7 Review of Safety

7.7 Additional Submissions/Safety Issues

7.7.1 Data Safety Monitoring Board (DSMB)

The DSMB will be responsible for assessing the safety of the interventions (17-HPC and vehicle) during the trial, and for monitoring the conduct of the clinical trial as it relates to the safety of the subjects and their fetus/infant in the trial.

For the purposes of the DSMB, safety data will be defined as:

- Maternal complications
- Adverse events
- Serious adverse events
- Fetal/infant death
- Neonatal morbidity

Data review meetings will be held at a minimum, once per year for review of the maternal complication, adverse/serious adverse event, and fetal/infant death data. When approximately 20%, 40% and 60% of randomized subjects have delivered and neonatal data have been entered into the study database and necessary (as determined by the project statistician) queries resolved, neonatal morbidity will be reviewed. More frequent meetings may be requested by the DSMB chair or the Applicant if it is warranted by outcomes seen in the safety data review.

7.7.2 Recent Safety Literature

Several publications have shed some further light on safety of 17-HPC in pregnant women:

- **Miscarriages/Stillbirths**
    - A randomized, double blinded, placebo controlled, multicenter trial to test whether 17-HPC would reduce neonatal morbidity by increasing the gestational age at delivery in triplet pregnancies. Prophylactic treatment with 17-HPC *was associated with increased midtrimester loss* (Combs, 2010[22]); however, the proportion of *mothers* who lost 1 or more fetuses was 5/56 (9%) in the 17-HPC group vs. 0/25 in the placebo group (P = .32) was not significant, compared to the proportion of *fetuses* lost was 13/168 (*%) and 0/75 respectively (P<.02).
    - A randomized, double blinded, placebo controlled, multicenter trial to test whether prophylactic 17-HPC given to mothers with twin pregnancy will reduce composite neonatal morbidity by decreasing the rate of preterm delivery. The authors state "contrary to our previous report that 17P was associated with an increased risk of midtrimester loss in triplet pregnancies, we found no such association in this trial of twin pregnancies." (Combs, 2011[23])
    - The NICHD MFMU Network conducted a randomized placebo-controlled, multicenter trial in twin pregnancies where 17-HPC was initiated between 16^0 and 20^6 weeks. There was *no trend in miscarriage or stillbirth* comparing 17-HPC to placebo. (Rouse 2007[24]).
    - A meta-analysis of four published studies showed a possible association of 17-HPC with miscarriage, demonstrating a non-significant odds ratio of 1.30 (95% confidence interval 0.61 to 2.74) (Keirse 1990[25]).
- **Diabetes in Pregnancy**.
    - A secondary analysis of 2 double-blind randomized placebo-controlled trials of 17-HPC given to 1094 women (616 received 17-HPC) at risk for preterm delivery. Administration of 17-HPC was *not associated with higher rates of gestational diabetes* in either singleton or twin pregnancies (Gyamfi 2009[26]).
    - Singleton gestations in women having a history of preterm delivery were identified from a database containing prospectively collected information from women receiving outpatient nursing services related to a high risk pregnancy. Patients with preexisting diabetes were excluded. The incidence of Gestational Diabetes Mellitus (GDM) was compared between patients who received prophylactic intramuscular 17-HPC (250-mg weekly injection initiated between 16.0 and 20.9 weeks gestation) and those who did not. Maternal BMI and age were similar. The incidence of GDM was 12.9% in the 17-HPC group (n=557) compared with 4.9% in control subjects (n=1,524, $p < 0.001$) (Rebarber 2007[27]).
    -

7.7.3 Follow-up Study (17P-FU-004)

The Applicant also will conduct another prospective, non-interventional follow-up study of children aged 18 to 24 months, born to mothers who received 17-HPC or placebo in the Confirmatory study (17P-FU-004). The Division conveyed their acceptance of the protocol for this study during a meeting on 17 December 2009. The Protocol was revised on January 7, 2011, and will be resubmitted following any further Division comments in March 2011, per the agreed-upon PMR timelines. A summary of this protocol is described below.

The primary objective of this study is to determine whether there is a difference in the developmental status between children aged 23 to 25 months whose mothers received 17-HPC or vehicle in the Confirmatory Trial (17-ES-003).

The study is a prospective, non-interventional follow-up study designed to provide a developmental assessment of children born to mothers who participated in the Confirmatory Trial. Subjects will be screened for developmental delay using the Ages and Stages Questionnaire (ASQ) version 3. Subjects who "score positive" (fall below the specified cutoff for developmental delay in any 1 of the 5 ASQ domains) will be referred for the Bayley Scales of Infant and Toddler Development (3rd edition), and a neurological examination. The subject population will be approximately 584 -750 children aged 23 to 25 months, born to mothers who participated in the Confirmatory Study. An illustration of how the Applicant attempted to estimate the number of subjects that may complete the study is presented in Table 12.

Table 12 Infant Follow-up Minimum Enrollment Estimate

	Percent	Number
A. 17P-ES-003 Study sample size		1707
B. Eligible subjects (live birth and not lost to follow up)	95%	1622
C. Subjects at participating sites	75% - 80%	1216 - 1297
D. Subjects at participating sites consented	75% - 80%	912 - 1038
E. Subjects at participating sites contact maintained	80% - 85%	730 - 882
F. Subjects at participating sites returning ASQ	80% - 85%	584 - 750

Source: Applicant's response to DRUP Requests from Teleconference of 5 January 2011

Safety assessments will include:
• Developmental assessment (ASQ).
• Secondary assessment(s) for ASQ screen positives will include the Bayley Scales and a neurological examination.

Enrollment will be sufficient to ensure that a completed ASQ will be obtained for 584 – 750 subjects. A completed ASQ obtained for 250 17-HPC subjects and 125 vehicle subjects will allow for an 88% power to detect a 15% absolute difference in the primary outcome rate using an alpha level of 0.05 and an outcome rate of 30% in the 17-HPC group.

On Jan. 5, 2011, the Division requested that Applicant offer enrollment to all offspring in the 17P-FU-004 study and the Applicant agreed to this on Jan 7, 2011. Based on the results of the NICHD study, the Sponsor expects that approximately 95% of the 1707 women who will be randomized in the 17P-ES-003 study will complete the study and have delivery data available on an infant that survives the neonatal period. Of these, the Sponsor expects approximately 75 - 80% to be at a site participating in the 17P-FU-004 study, which will result in approximately 584-750 subjects for this study.

Medical Officer's Comments:

- *The statistical rigor for this safety follow-up study is not as critical as the confirmatory study since the Division considers it mostly a descriptive study.*

7.7.4 Safety Update

The Applicant submitted a Safety Update for the period between 01 March 2009 and 29 October 2010, which reported blinded data from the ongoing Confirmatory trial.

Eight subjects experienced at least one SAE. A total of 12 SAEs were reported, 3 of which resulted in a fetal/neonatal death. There were no maternal deaths reported. Eight separate hospitalizations were required for 7 subjects while one subject (overdose) was not hospitalized. The three events resulting in fetal/neonatal death were: cardio-respiratory arrest related to severe prematurity (delivery at 21 weeks with a birth weight of 340 g; age <1 day), intrauterine death at 32 weeks 4 days, and miscarriage (19 weeks 3 days). Other non-pregnancy-related SAEs included: two cases of pancreatitis, and one case each of pneumonia, edema, migraine headache, and an increase in blood glucose. An overdose occurred in a subject who received a 5-mL rather than a 1-mL injection of study drug. This subject was discontinued from study treatment but continues to be followed for safety assessments. No adverse event related to the overdose has been experienced to date.

One subject was reported in the clinical database to have discontinued study medication due to a non-pregnancy-related AE. This subject was discontinued due to a mild rash at each injection site. Four doses of test injection and study medication were given and the rash resolved after approximately 1 – 1.5 weeks

8 Postmarket Experience

AERS Search

The Division of Pharmacovigilance 2 was asked to provide an update on adverse events reports submitted to the AERS system since the previous review of AERS done in June 2008. A single report subsequent to the previous cut-off date of May 27, 2008 was found. This concerned a 1985 pregnancy in a woman who used 17-HPC during gestational weeks 5-17, and gave birth to a male infant with microcephaly and monosomy of chromosome 8p. The woman had used alcohol heavily during pregnancy and she claimed that 17-HPC (Delalutin) had caused her to drink heavily, resulting in birth defects from alcohol. There have not been any other reports of 17-HPC causing alcohol abuse in either the AERS database or described in the literature.

9 Appendices

9.1 Labeling Recommendations

The Applicant's Label was reviewed by the Division and the following requests were sent to the Applicant:

- Replace the indication "for the prevention of preterm birth" with "to reduce the risk of preterm birth"
- Add the basis for effectiveness (surrogate endpoint of improvement in the proportion of women who deliver at < 37 weeks gestation in the clinical trial) to the "Indications and Usage" section.
- Add "caveats" about the reduction of preterm birth at <35 and <32 weeks gestation.
- Add "administer by a health care provider" to the "Dosage and Administration" section.
- Add thromboembolic disorders, allergic reactions, jaundice and hypertension to the "Warnings and Precautions" section.
- Restructure the "Adverse Reactions" section to place more emphasis on miscarriage and stillbirth, and add a separate table for illustration. Also, add "Adverse Reactions leading to Study Discontinuation" (urticaria, injection site pain) and "Serious Adverse Reactions" (pulmonary embolus, injection site cellulitis) to this section.
- Add "Makena is not intended for use during labor" to the "Use in Specific Populations" section.
- Revise the numbers in the efficacy table for clinical trial (17P-CT-002) in the "Clinical Studies" section to reflect the FDA's analysis of the data.

The Applicant agreed to all requested changes to the label (Package Insert). The Division requested that the Applicant submit a Patient Package Insert and this was submitted on 10/22/10. The Division added a section to describe the efficacy of Makena and a section to alert the patient to the potential risks of miscarriage and stillbirth.

9.2 Bibliography

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/s/

BARBARA D WESLEY
02/03/2011

LISA M SOULE
02/03/2011

I concur with Dr. Wesley's recommendation that NDA 21-945 be approved under Subpart H for the indication to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

Division Director Summary Review for Regulatory Action

Date	January 23, 2009
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 21-945 (complete response submission)
Applicant Name	Cytec Corporation
Date of Submission	April 25, 2008
PDUFA Goal Date	January 25, 2009 (with 3-month extension)
Proprietary Name / Established (USAN) Name	Gestiva Hydroxyprogesterone caproate
Dosage Forms / Strength	Intramuscular injectable/250 mg/mL
Proposed Indication	Prevention of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth
Proposed Regimen	One mL (250 mg/mL) once weekly
Action	***Complete Response (non-Approval) (see Section 13.1)***

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer Review	Barbara Wesley, MD (primary reviewer)
Statistical Review	Lisa Kammerman, PhD/Mahboob Sobhan, PhD
Pharmacology Toxicology Review	Alexander Jordan, PhD/Lynnda Reid, PhD
CMC Review/ONDQA	Donna Christner, PhD/Moo-Jhong Rhee, PhD
Microbiology Review	John Metcalfe, PhD/James McVey, PhD
Clinical Pharmacology Review	Doanh Tran, PhD/Myong-Jin Kim, Pharm.D
DDMAC	Not required for this review cycle
DSI	Dylan Dalin Yao MD, PhD
CDTL/Medical Team Leader	Lisa Soule, MD
OSE/DMEPA	Felicia Duffy, RN, BSN/Kellie Taylor, PharmD Denise Toyer, PharmD/Carol Holquist, RPh

OND	Office of New Drugs
DDMAC	Division of Drug Marketing, Advertising, and Communication
OSE	Office of Surveillance and Epidemiology
DMEPA	Division of Medication Errors Prevention and Analysis
DSI	Division of Scientific Investigations
CDTL	Cross-Discipline Team Leader

1. INTRODUCTION

Preterm birth, defined as birth prior to 37 completed weeks of gestation, is a significant public health problem in the United States, with an increasing prevalence currently estimated to affect 12% of all births. Although there are a number of diagnostic tests proposed to identify women at risk for preterm labor and medications used off-label to treat preterm labor, there are no data indicating a benefit on neonatal morbidity or mortality from any of these interventions. Rates of preterm birth in the United States differ profoundly among ethnic groups.

Currently there is no approved drug product in the U.S. for prevention of preterm birth; however, hydroxyprogesterone caproate (HPC), also known as 17α-hydroxyprogesterone caproate (17OHP-C), is being compounded by pharmacists and is being used widely for prevention of preterm birth in women at high risk. The medical need for an approved drug product for prevention of preterm birth is particularly acute because there also are no approved drug products currently marketed in the United States for the treatment of preterm labor. Although several drug products with tocolytic properties (i.e., stopping uterine contractions) are used off-label for treatment of preterm labor, randomized controlled trials have failed to demonstrate that these drugs improve perinatal outcomes.

In 2003, the findings from a multicenter, randomized, vehicle-controlled, double-blind clinical trial of HPC in women at high risk for preterm birth were published.[1] This trial was sponsored by the National Institute for Child Health and Human Development (NICHD). The trial was conducted for the NICHD by the Maternal-Fetal Medicine Units (MFMU) Network, which at that time consisted of approximately 19 university-based clinical centers in the U.S. This study (hereafter referred to as Study 17P-CT-002) showed a reduction in preterm births < 37 weeks gestation in women with a prior spontaneous preterm birth (a population at high risk for a recurrent preterm birth).

NDA 21-945 for the use of HPC for the prevention of preterm birth in women with a prior history of at least one spontaneous preterm birth was first submitted to the Division of Reproductive and Urologic Products (DRUP) in April 2006. The clinical component of NDA 21-945 was based largely on the data from the NICHD clinical trial (Study 17P-CT-002) and a follow-up safety study (Study 17P-FU) that enrolled children whose mothers had participated in Study 17P-CT-002. Following a priority review of NDA 21-945, which included presentation of the NDA to an Advisory Committee, the Application received an Approvable Action in October 2006. The Application was not approved because of clinical, non-clinical toxicology, and chemistry, manufacturing, and control (CMC) deficiencies.

In the current submission, the Applicant has attempted to adequately address all of the deficiencies listed in the October 20, 2006, Approvable Letter. As such, the Application included (1) a draft clinical protocol to confirm and expand upon the efficacy and safety findings from Study 17P-CT-002 (see Section 7 of this Memo), (2) a final report from a non-clinical multi-generational reproductive toxicology study (see Section 4), and (3) additional CMC information (see Section 3).

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The information provided in the Applicant's current submission adequately addresses the non-clinical toxicology and CMC deficiencies but does not adequately address the clinical deficiencies. The Applicant has not provided sufficient documentation that the proposed confirmatory clinical trial is feasible and is likely to be completed successfully, particularly if the trial is to be conducted primarily in the U.S. Because the clinical deficiencies have not been adequately addressed in the current submission, the regulatory action for the current submission will be non-Approval (i.e., a Complete Response action). Both the primary Medical Reviewer and the Cross Discipline Team Leader/Medical Team Leader concur with this non-Approval action.

2. BACKGROUND

2.1 Description of Drug Product

Hydroxyprogesterone caproate was approved by the Food and Drug Administration (FDA) in 1956 for use in pregnant women (NDA 10-347; Delalutin®). The approved indications included the treatment of habitual and recurrent abortion, threatened abortion, and post-partum "after pains." This approval was based largely on safety considerations in that it occurred prior to the FDA Drug Amendment of 1962, which required that drugs must have substantial evidence of efficacy in addition to evidence of safety in adequate and well-controlled trials. In 2000, the FDA withdrew approval for Delalutin. This action was taken at the request of the holder of the NDA. The action was not taken because of safety concerns.

The proposed drug product contains 250 mg HPC/mL in castor oil. The proposed dosing regimen for the prevention of preterm birth in high risk pregnant women is a once-weekly 1 mL intramuscular injection beginning between 16 weeks 0 days (16^0 weeks) gestation and 20 weeks 6 days (20^6 weeks) gestation and used through 36^6 weeks gestation or birth.

2.2 Regulatory History

2.2.1 Background

After data from Study 17P-CT-002 were published in the New England Journal of Medicine, Adeza Biomedical (the original Applicant for NDA 21-945) met with DRUP to discuss the possibility of using these data as the basis for an NDA for HPC for the indication of prevention of preterm birth in pregnant women with a previous spontaneous preterm birth. Because Study 17P-CT-002 had not been designed as a clinical trial to support marketing approval of HPC, DRUP conveyed several recommendations and concerns to the Applicant during this and subsequent meetings. These recommendations and/or concerns included:

- The lack of follow-up data, beyond the period of initial hospital assessment, of children whose mothers had received HPC for the prevention of preterm birth. DRUP requested that the Applicant obtain follow-up developmental and safety data through at least 2 years of age for children whose mothers had participated in Study 17P-CT-002.
- Clinical trial data supporting the safety and efficacy of HPC for the proposed indication would be derived primarily from only a single adequate and well-controlled trial. The Applicant was informed that generally data from 2 adequate and well controlled trials was required for marketing approval.

In support of their original NDA, the Applicant submitted data from 2 active treatment clinical trials and a follow-up safety study (see Table 1). The primary source of data in support of the efficacy and safety of HPC, however, was Study 17P-CT-002.

Table 1 Clinical Studies of HPC in Original Submission of NDA 21-945

Protocol # / Status	Study Design	Study Population	Treatment Dose	Duration of Drug Treatment	Number of Subjects Enrolled	Number of Black/ Non-Black Subjects	Mean Age (Range)
17P-IF-001 Terminated Mar 1999[A]	Double-blind, Vehicle-controlled, Randomized 2:1 HPC to Vehicle	Pregnant women with previous spontaneous preterm birth	250 mg HPC per week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 36^6 wks gestation or delivery	Total: 150 HPC: 94 Vehicle: 56	Total: 95/55 HPC: 54/40 Vehicle: 41/15	26.2 yr (17, 42)
17P-CT-002 Completed Aug 2002[B]	Double-blind, Vehicle-controlled, Randomized 2:1 HPC to Vehicle	Pregnant women with previous spontaneous preterm birth	250 mg HPC per week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 36^6 wks gestation or delivery	Total: 463 HPC: 310 Vehicle: 153	Total: 273/190 HPC: 183/127 Vehicle: 90/63	26.2 yr (16, 43)
17P-FU Completed Nov 2005	Observational long-term safety follow-up for Study 17P-CT-002	Infants discharged live in Study 17P-CT-002	None	No study treatment was administered	Total: 278 HPC: 194 Vehicle: 84	Total: 152/126 HPC: 105/89 Vehicle: 47/37	47.4 mo (30, 64)

[A] Study 17P-IF-001 was terminated early by the Sponsor when the manufacturer recalled the study drug because of reduced potency. Of the 150 subjects, 104 subjects (65 randomized to HPC and 39 randomized to vehicle) had ended their treatment prior to the study termination because (1) they had completed treatment with study drugs (i.e., completed study treatment to 36^6 weeks of gestation or delivery had occurred) or (2) they had withdrawn prematurely for reasons other than recall of study drugs.

[B] An independent Data and Safety Monitoring Committee (DSMC) reviewed the study data after 400 subjects had completed the study. Based on that interim dataset, the primary endpoint, birth $<37^0$ weeks of gestation, was significantly reduced and the p-value was below the p-value specified in predefined stopping rules. The DSMC recommended that enrollment in the study be stopped, so that no new subjects would be assigned vehicle. By the time the study was stopped, 463 subjects had been enrolled, which was 92.5% of the proposed sample size of 500 subjects.

Source: Table 2, pg. 20 of original primary Medical Review for NDA 21-945 (2006).

2.2.2 Efficacy Findings for Study 17P-CT-002 from First Review Cycle

2.2.2.1 Study Objectives

The primary protocol-defined objective for Study 17P-CT-002 was to determine if treatment with HPC, initiated between 16^0 and 20^6 weeks gestation, compared to treatment with vehicle, reduced the risk of preterm birth (birth $<37^0$ weeks gestation) in women who had previously experienced a prior spontaneous preterm birth. At the request of DRUP, the following secondary endpoints were added to the analyses of the study:

- Whether treatment with HPC, compared to vehicle, reduced the risk of preterm birth $< 35^0$ and $< 32^0$ weeks gestation.

- Whether treatment with HPC reduced overall neonatal morbidity/mortality based on a composite measure of neonatal morbidity and mortality. The composite was based on the proportion of infants who experienced one or more of the following: death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis, or necrotizing enterocolitis (NEC).

Division Director's Comment

- *The Division made the request to determine the reduction in preterm births at <35 and <32 weeks gestation because of the increased morbidity/mortality associated with premature births at these ages.*

2.2.2.2 Percentages of Subjects with Preterm Births

The percentages of subjects with a preterm birth in the HPC and vehicle (placebo) treatment groups and the mean treatment differences at (1) < 37^0 weeks gestational age (protocol defined primary endpoint) and (2) < 35^0 and < 32^0 weeks gestational age (secondary endpoints) are listed in Table 2.

Table 2 Proportion (95% Confidence Interval) of Subjects with Preterm Births (FDA Analysis)

Gestation Age at Birth	HPC [A] (N=310)	Vehicle (N=153)	Mean Treatment Differences [95% Confidence Interval] [B]
	Percent of Preterm Births		
< 37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
< 35^0 weeks	21.3	30.7	-9.4% [-18.7%, -0.2%]
< 32^0 weeks	11.9	19.6	-7.7% [-16.1.%, -0.3%]

[A] Four HPC treated patients were lost-to-follow-up. They are counted as deliveries at their gestational ages at time of last contact (18.6, 22.0, 34.4, and 36.6 weeks).
[B] To preserve the overall type I error rate of 0.05, the adjusted confidence intervals (equivalent to a 96.6% confidence interval) use the final p-value boundary of 0.0345.
Source: Table 3.1, FDA statistical review, October 19, 2006.

Division Director's Comments

- *There was a statistically significant treatment effect of HPC in reducing the percentage of subjects with a recurrent preterm birth at < 37, < 35, and < 32 weeks gestational age after adjusting for the 2 interim analyses and the final analysis to preserve the overall type I error rate of 0.05. Based on an analysis by the Applicant, the benefit of treatment for preterm birth of < 37 weeks gestation appeared to remain consistent over varying levels of maternal risk, as measured by maternal race, number of prior preterm births, and gestational age of qualifying preterm birth.*
- *The reduction in recurrent preterm births for < 37 weeks gestation was strongly statistically significant. However, the reduction in preterm births at earlier gestational ages (i.e., < 35 weeks and < 32 weeks), although statistically significant, did not meet the level of statistical significance generally expected to support approval of a drug product based on the findings from a single clinical trial.*

Upon recognition that a single center, the University of Alabama, had contributed 27% of subjects in Study 17P-CT-002, DRUP requested that the Applicant provide a table analyzing the primary and key secondary endpoints for the Alabama site alone, for all the other sites, and for all centers combined. Results of this analysis are presented in Table 3.

Table 3 Percentages of Preterm Births – Effect of Largest Center on Outcomes

Gestation (weeks)	Percentage of Preterm Births								
	University of Alabama			All Other Centers Combined			All Centers		
	HPC (n=86)	Vehicle (n=40)	Diff.	HPC (n=224)	Vehicle (n=113)	Diff.	HPC (n=310)	Vehicle (n=153)	Diff.
< 37	26.7	45.0	***-18.3***	41.1	58.4	***-17.3***	37.1	54.9	***-17.8***
< 35	17.4	27.5	***-10.1***	22.8	31.9	***-9.1***	21.3	30.7	***-9.4***
< 32	10.5	25.0	***-14.5***	12.5	17.7	***-5.2***	11.9	19.6	***-7.7***

Source: Applicant's submission of October 10, 2006.

Division Director's Comments

- *The rates of preterm birth at < 37 and < 35 weeks gestation are numerically lower in both the HPC and vehicle groups at the University of Alabama compared to the rates at the other centers combined. The treatment effects (i.e., the differences in the percentages of preterm births between HPC and vehicle groups), however, at < 37 and < 35 weeks are similar at the Alabama site, the other centers combined, and all centers. This analysis indicates that the results at the Alabama site, per se, do not appear to be responsible for the overall observed treatment effect at < 37 and < 35 weeks gestation.*
- For < 32 weeks gestation, however, there was an apparently greater benefit of treatment at the Alabama site than at the other centers combined (treatment effect of -14.5% [Alabama] vs. -5.2% [other sites combined]). Thus, it may not be appropriate to extrapolate the mean treatment effect observed at < 32 weeks gestation to pregnant women, in general, at high risk for a recurrent preterm birth.

2.2.2.3 Composite Index of the Neonatal Morbidity/Mortality

There was a lower proportion of subjects in the HPC group (11.9% HPC group vs. 17.2% vehicle group) who experienced at least one event of the composite morbidity/mortality index, but this difference was not statistically significant. There was also a numerical decrease in the neonatal mortality rate (2.6% in the HPC group vs. 5.9% in the placebo group), but this difference also was not statistically significant.

Division Director's Comment

- *The clinical trial was not powered to show a reduction in infant morbidity/mortality.*

2.2.3 Safety Findings from First Review Cycle

The safety findings, based on review of the original NDA submission, have been presented in detail in the primary Medical Review of Dr. Wesley for the original submission.

There were no safety findings in the original NDA submission of April 2006, based on data from Study 17P-CT-002 (the primary source of efficacy and safety data), supportive Study 17P-IF-001, Study 17P-FU (follow-up of children whose mothers participated in Study 17P-IF-001), or published medical literature that would have precluded approval of HPC for the proposed indication.

The only significant clinical finding of concern in the original submission was an apparent increase in early pregnancy loss in the HPC treated subjects in Study 17P-CT-002. There was a trend toward an increase in the second trimester miscarriage rate (pregnancy loss prior to

20 weeks of gestation) and a suggestion of an increase in stillbirth rate (death of a fetus prior to or during delivery) in the HPC group. The numbers of miscarriages, stillbirths, and neonatal deaths in each of the treatment groups are listed in Table 4. Conversely, the incidence of neonatal deaths was numerically reduced by slightly more than 50% in the HPC group (2.6% vs. 5.9%), but the difference was not statistically significant. The overall incidence of combined fetal and neonatal mortality from the onset of treatment to delivery was similar in the 2 treatment groups (19 of 306 [6.2%] in the HPC group and 11 of 153 [7.2%] in the vehicle group).

Table 4 Miscarriages, Stillbirths, and Neonatal Deaths (Study 17P-CT-002)

Pregnancy Outcome	HPC N=306 n (%) [A]	Vehicle N=153 n (%) [A]	Nominal P-value [B]
Miscarriages <20 weeks gestation	5 (2.4)[C]	0	0.17
Stillbirth	6 (2.0)	2 (1.3)	0.72
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.12
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.69**

[A] Percentages are based on number of enrolled subjects and not adjusted for time on drug.
[B] No adjustment for multiple comparisons.
[C] Percentage adjusted for the number of at-risk subjects (n=211) enrolled at < 20 weeks gestation.
Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

Division Director's Comments

- *A similar trend toward an increase in the rates of miscarriage and possibly stillbirth was not observed in the HPC treatment group in the smaller supportive Study 17P-IF-001.*
- *These findings were presented to the members of the Advisory Committee for Reproductive Health Drugs. The recommendation of the majority of the members was that this observation required further investigation, but the investigation could be conducted post-approval. A majority of the committee members also voted that no additional clinical safety data were required prior to approval of HPC for the prevention of preterm birth in women with a history of a prior spontaneous preterm birth (see Section 2.2.4).*

2.2.4 Advisory Committee Recommendations

The original Application was presented to the Advisory Committee for Reproductive Health Drugs (ACRHD) on August 29, 2006, during the original review cycle. The Advisory Committee was asked to vote on several issues that included the following:

Issue 1. Is a reduction in preterm birth prior to 37, 35, or 32 weeks gestation an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity?

- The Committee stated that a reduction in preterm birth < 37 weeks was not an adequate surrogate (yes: 5, no: 16) but that reductions in preterm birth < 35 weeks (yes: 13, no: 8) and < 32 weeks (yes: 20, no: 1) were adequate surrogates.

Issue 2. Do the data provide substantial evidence that HPC prevents preterm birth earlier than either 35 or 32 weeks gestation?

- The Committee (by a small majority) indicated that the data provided substantial evidence that HPC prevents preterm birth < 35 weeks (yes: 12, no: 9) but did not provide substantial evidence for < 32 weeks (yes: 7, no: 14).

Issue 3. Is further study needed to evaluate the potential association of HPC with increased risk of second trimester miscarriage and stillbirth and if so, should this information be obtained prior to approval for marketing or post-approval*?*

- The Committee was unanimous in its recommendation that further study was needed (yes: 21, no: 0) but a majority felt that this information could be obtained post-approval (pre-approval: 8, post-approval: 13).

Issue 4. Are the overall safety data obtained in Studies 17P-CT-002 and 17P-IF-001 and Study 17P-FU (long-term follow-up study) adequate and sufficiently reassuring to support marketing approval of HPC without the need for additional pre-approval safety data?

- A majority of the Committee voted that the existing safety data were sufficient to support marketing approval of HPC without the need for additional pre-approval safety data (yes: 13, no: 8).

Division Director's Comments

- *Overall, a majority of the Committee members indirectly expressed support for approval of HPC based on their votes regarding the following 3 issues:*
  - *Thirteen of the 21 members voted that a reduction in preterm birth < 35 weeks was an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity;*
  - *Twelve of the 21 members voted that the Applicant's data provided substantial evidence that HPC prevents preterm birth < 35 weeks gestation; and*
  - *Thirteen of the 21 members voted that the existing safety data were sufficient to support marketing approval of HPC without the need for additional pre-approval safety data.*
- *The committee also was unanimous in recommending that further study was needed to evaluate the potential association of HPC with increased risk of second trimester miscarriage and stillbirth, but a majority (13 of 21 members) stated that this information could be obtained post-approval.*
- *These recommendations, in my opinion, could support approval of HPC under Subpart H 21 CFR 314.510. Approval would be based on a surrogate of neonatal morbidity and mortality (reduction in births < 35 weeks gestation). Confirmation of the finding of a reduction in preterm births < 35 weeks gestation and further data regarding the impact of treatment with HPC on neonatal morbidity and/or mortality, in an adequately powered study, would be obtained in a confirmatory study (see Section 7.1) that the Applicant will be asked to initiate prior to approval under Subpart H and will complete post-approval.*

2.2.5 Regulatory Action at End of First Review Cycle

2.2.5.1 Basis for Approvable Action

The Applicant's single Phase 3 clinical trial demonstrated a statistically strong reduction in the incidence of preterm births prior to 37 weeks gestational age, the protocol-defined primary endpoint. However, the reduction in preterm births at earlier gestational ages (i.e., < 35 weeks

and < 32 weeks), although statistically significant, did not meet the level of statistical significance generally expected to support approval of a drug product based on the findings from a single clinical trial. The trial also was not designed or powered to demonstrate a reduction in major neonatal morbidities and/or neonatal mortality. However, a majority of the members of the Advisory Committee believed that preventing preterm birth at < 35 and < 32 weeks of gestation represented an adequate surrogate for a reduction in neonatal morbidity and mortality. A majority of committee members also thought that there was a significant reduction in preterm births < 35 weeks gestation in Study 17P-CT-002.

The clinical and statistical reviewers of this Application raised questions as to whether the evidence of efficacy from this single Phase 3 study was adequate and sufficiently convincing to support approval. An Approvable Letter was issued that defined additional information required to obtain approval to market HPC for the indication of prevention of preterm birth in pregnant women with a history of a prior preterm spontaneous birth. The Approvable Letter conveyed to the Applicant that if outstanding deficiencies were satisfactorily addressed (see Section 2.2.5.2), approval under Subpart H 21 CFR 314.510 could be a possibility.

2.2.5.2 Content of Approvable Letter

The deficiencies and information needed to address the deficiencies outlined in the Approvable Letter of October 20, 2006, included the following:

Clinical

1. Further study is needed to provide confirmatory evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly, or through a well-established surrogate, such as the rate of preterm birth prior to 35 and 32 weeks of gestation.
2. There are insufficient data to evaluate a potential association of hydroxyprogesterone caproate (HPC) with an increased risk of early fetal loss (second trimester miscarriage and stillbirth).

Information needed to address the clinical deficiencies

1. Submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of HPC for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510. If a placebo-controlled trial is determined not to be feasible, provide alternative study design proposals.
2. Provide a draft protocol to evaluate the potential association of HPC with increased risk of second trimester miscarriage and stillbirth. This could be assessed as a part of the confirmatory efficacy study referred to in Item No. 1 above.

Pharmacology and Toxicology

There is a lack of nonclinical data from a multi-generational reproductive toxicology study for this product.

Information needed to address the toxicology deficiency

A GLP-compliant, multigenerational reproductive toxicology study needs to be performed, evaluating all stages of pregnancy during which dosing will be administered

in humans. The study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including learning, behavior, and reproductive function, in offspring exposed *in utero*. At the time of a Complete Response submission to this approvable letter, provide, at a minimum, an unaudited interim final report of the requested study.

Chemistry, Manufacturing and Controls (CMC)

1. Significant degradation was observed for the light-stressed drug product sample with respect to content (assay) during the HPLC method validation studies. Thus, the drug product appears to be photosensitive; however, the resulting photo-degradation products are not detectable by your HPLC method.
2. Given the results from your photo-stability study in which both the Stage 1 (fully exposed to light) and Stage 2 (enclosed in a chipboard box) samples showed decreases in content (assay) from that of the control (wrapped in foil) without corresponding increases in impurities by your HPLC method, you have not demonstrated that the secondary packaging provides adequate light protection for the drug product.
3. Your proposed expiration date of 24 months for the drug product is not acceptable based on the stability data included in your application to date.

Information needed to address the CMC deficiencies

1. Since you cannot account for the degradation of the active ingredient under light-stress conditions by your HPLC method, you should develop a supporting method that can adequately detect and quantitate the potential photo-degradation products. The drug product specifications should include limits for any potential impurities observed using the new method, and a detailed description of the new analytical procedure with appropriate validation should be provided.
2. Alternative primary and/or secondary packaging should be used to protect the drug product from light. A description and justification for the new packaging system should be submitted with appropriate letters of authorization. In addition, you should revise the drug product labeling to state that the vials should be protected from light.
3. Based on the limited stability data provided in the application and the out-of-specification (OOS) results for particulate matter observed at accelerated conditions, an expiration date of NMT (b) (4) would be appropriate for the drug product when stored at controlled room temperature, protected from light. You are encouraged to determine the cause of the OOS results for particulates under accelerated conditions, and if necessary, you should consider a different container closure for storage of your drug product.

The letter also outlined additional issues that would need to be addressed postmarketing, if the product were to be approved:

Clinical (postmarketing requests)

1. Completion of the additional efficacy and safety study(ies) requested above under the description of clinical deficiencies will be required as a condition of an approval under Subpart H 21 CFR 314.510 (Item No. 1 above under clinical deficiencies) or as a formal phase 4 commitment (Item No. 2 above under clinical deficiencies).

2. Long-term post treatment safety data (at least through puberty) from children whose mothers had been treated with HPC is lacking in the NDA. This information is requested and could be obtained through the establishment of a surveillance program (e.g., registry) to evaluate the effects of prenatal exposure in adolescents and young adults. Submit your proposal as to how these data would be obtained. (See Division Director's Comments, Section 7.3).
3. Additional developmental assessment is needed of children at ages 18-24 months whose mothers had been treated with HPC. This assessment could be obtained from the offspring of women enrolled in the confirmatory efficacy study or the safety study addressing early fetal loss. Children who screen positive for developmental delay should have a formal psychometric assessment and an additional assessment by a neurologist.

2.3 Dispute Resolution Request by Applicant

Following receipt of the Approvable Letter, the Applicant filed a Formal Dispute Resolution Request to the Office of Drug Evaluation III (ODE III) on March 16, 2007. Three requirements in the Approvable Letter were disputed: the need for a reproductive toxicology study, the need for a multicenter confirmatory efficacy trial, and the need for preapproval submission of a protocol to evaluate the potential increased risk of early fetal loss. Dr. Daniel Shames, Deputy Director of ODE III reviewed the Applicant's arguments and wholly concurred with the Division's decisions as described in the Approvable Letter. This decision was conveyed to the Applicant on April 12, 2007.

3. CMC (CURRENT SUBMISSION)

In the Approvable Letter of October 20, 2006, 3 CMC deficiencies were listed (Section 2.2.5). These deficiencies concerned (1) failure to detect photo-degradation products by the Applicant's HPLC method, (2) failure to demonstrate that the secondary packaging provided adequate light protection for the drug product, and (3) lack of adequate data to support a product expiration date of 24 months. In her review of the current submission, the primary Chemistry Reviewer, Donna Christner, PhD, stated that the 3 deficiencies were adequately addressed. During the current review cycle, however, an issue was raised concerning microbiological stability of the product once the product (sterile vial) was penetrated. The issue was consulted to Microbiology, which determined that the data provided by the Applicant were adequate to support an in-use shelf-life of 5 weeks once the stopper was penetrated during actual use.

The primary Chemistry Reviewer made the following statement and recommendation in her review, signed on December 22, 2008:

> *"This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for APPROVAL."*

Division Director's Comments

- *I concur with the assessment/recommendation made by Dr. Christner. There are no outstanding CMC issues.*
- *An in-use shelf-life of 5 weeks once the vial stopper is penetrated by a syringe needle will be reflected in the DOSAGE and ADMINISTRATION section of labeling.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY (CURRENT SUBMISSION)

The Approvable Letter of October 20, 2006, listed "a lack of nonclinical data from a multi-generational reproductive toxicology study" as a deficiency that would need to be resolved prior to approval of HPC for the proposed indication. A submission to the NDA, received on June 16, 2008, contained the final Report for a multigenerational study in rats in which offspring exposed *in utero* were evaluated for potential effects on development, learning, and behavior. The study was conducted under Good Laboratory Procedures and was also audited by FDA inspectors. The study did not find any potential adverse effects on neurologic or reproductive development of offspring exposed to HPC *in utero*.

Unrelated to the multi-generational reproductive toxicology study was a report of embryolethality in rhesus monkeys receiving HPC at doses equivalent to the human dose. Similar findings were not observed in Cynomolgus monkeys or rodents receiving HPC. The Pharmacology/Toxicology Team Leader, Dr. Reid, stated in her NDA memo that this finding of embryolethality "does not appear to be a risk factor in humans."

The primary Pharmacology/Toxicology Reviewer, Alexander Jordan, PhD, made the following recommendations in his primary review:

A. Recommendation on approvability: "*I recommend approval of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth."*
B. Recommendation for nonclinical studies: "*none*."
C. Recommendations on labeling: Several labeling recommendations were made that will be incorporated into final labeling in the next review cycle should the product be approved for the proposed indication.

Division Director's Comment

- *I concur with the assessments and recommendations of Drs. Jordan and Reid.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS (CURRENT SUBMISSION)

The Approvable Letter of October 20, 2006, listed 3 Clinical Pharmacology issues that would need to be addressed post-approval; the Applicant has attempted to address these in the protocol for the proposed confirmatory efficacy and safety study or by submitting results from an ongoing NIH-sponsored pharmacokinetic trial that is studying HPC in pregnant women.

The primary Clinical Pharmacology Reviewer, Doanh Tran, PhD., stated the following in his review dated August 26, 2008:

> *"The Office of Clinical Pharmacology/Division of Clinical Pharmacology III finds NDA 21-945 acceptable provided the labeling comments and Phase IV commitment requests are adequately addressed."*

In an addendum to his review, dated January 15, 2009, Dr. Tran made the following two Phase 4 requests:

> *"The sponsor will provide data characterizing the pharmacokinetics (PK) of 17 α-hydroxyprogesterone caproate (17-HPC) and its metabolites in plasma and urine in pregnant women throughout different gestational stages."*

"The sponsor will conduct an in vitro study using human hepatocytes to determine whether 17-HPC induces or alters the metabolic activities of CYP1A2, CYP2A6, and CYP2B6."

Division Director's Comment

- I concur with the recommendation and Phase 4 requests from Dr. Tran.

6. CLINICAL MICROBIOLOGY (CURRENT SUBMISSION)

Microbiology was consulted regarding 2 issues. Regarding the first issue, John Metcalfe, PhD., reviewed a major amendment to the submission (change in (b) (4)) and recommended approval on the basis of microbiological product quality. He noted that "The proposed changes to the (b) (4) sequence do not adversely affect the microbiological quality of the subject drug product." The second issue, which was identified during review of the Application, concerned the microbiological stability of the product once the product (sterile vial) was penetrated. James McVey, PhD, concluded the microbiology data provided by the Applicant were adequate to support an in-use shelf-life of 5 weeks once the vial stopper was penetrated in actual use. Product labeling will reflect this 5-week duration of in-use shelf life.

7. CLINICAL/STATISTICAL-EFFICACY (CURRENT SUBMISSION)

To address the clinical issues in the Approvable Letter of October 20, 2006, the Applicant's Complete Response submission contained the protocol for a confirmatory efficacy and safety study, along with a discussion of the likely feasibility of conducting the study. The Applicant also provided a draft protocol for an infant follow-up study, and a discussion of a proposed follow-up study of exposed offspring once they reached adolescence.

7.1 Confirmatory Efficacy and Safety Study

The Applicant provided an initial protocol in the Complete Response submission and subsequently submitted several revisions to the protocol in response to recommendations made by DRUP Clinical and Statistical reviewers. The description of the protocol that follows is based upon the draft Protocol submitted electronically on January 15, 2009, which is entitled "*A Multi-Center, Randomized, Double-Blind Study of 17-α-Hydroxyprogesterone Caproate (17-P) versus Placebo for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous Preterm Delivery*," hereafter referred to as the "*Confirmatory Protocol*."

7.1.1 General Study Design

The *Confirmatory Protocol* is a multicenter, international, randomized, double-blind, vehicle-controlled study. The study will enroll 1,707 women aged 16 and above with a singleton gestation and a history of a previous singleton spontaneous preterm birth, randomized in a 2:1 ratio to treatment with HPC (250 mg) or vehicle (castor oil, hereafter referred to as placebo). Subjects will receive once weekly IM injections of Study Drug from the time of randomization (which will occur between 16^0 to 20^6 weeks of gestation) through 36^6 weeks of gestation or delivery. Maternal subjects will be followed until the later of 30 days after the last dose of study drug or discharge from the delivery hospitalization; neonates will be followed until 28 days of life, with those remaining hospitalized at 28 days post birth to be followed until the earlier of discharge or 120 days of life. Maternal subjects who discontinue study drug will remain in the study, and, at a minimum, delivery outcome data will be obtained.

7.1.2 Study Objectives and Endpoints

The **primary objective** of the *Confirmatory Study* is to determine if treatment with HPC, compared to placebo, reduces the rate of preterm birth < 35^0 weeks of gestation. The **key secondary objective** is to determine if treatment with HPC, compared to placebo, reduces the rate of neonatal morbidity/mortality, as measured by a composite index. The elements of the neonatal morbidity/mortality index are:

- Neonatal death
- Grade 3 or 4 intraventricular hemorrhage (IVH)
- Respiratory distress syndrome (RDS)
- Bronchopulmonary dysplasia (BPD)
- Necrotizing enterocolitis (NEC)
- Proven sepsis

Additional secondary objectives include:

- *Exclusion of a doubling of the risk of fetal/early infant death or stillbirth in the HPC arm as compared to the placebo arm*
- Determination as to whether HPC, compared to placebo, reduces the rate of preterm birth < 32^0 weeks gestation
- Determination as to whether HPC, compared to placebo, reduces the rate of stillbirths (including fetal losses) from 20 weeks of gestation onward
- Determination as to whether HPC, compared to placebo, reduces the rate of neonatal death
- Evaluation of PK/PD parameters for HPC in a subset of 450 subjects stratified by BMI

7.1.3 Statistical Analyses

The primary statistical analysis is hierarchical to protect against type 1 error. The statistical analysis for the key secondary objective will therefore be performed only if the primary endpoint of preterm birth < 35 weeks attains statistical significance.

According to the Applicant, the proposed sample size will provide 98% power to detect a 30% relative reduction (30% to 21%) in the rate of preterm birth at < 35 weeks with an alpha level of 0.05%. The study will also have 90% power to detect a 35% relative reduction (17% to 11%) in the rate of adverse outcomes, based on the composite neonatal index. The power to rule out a doubling of risk of fetal/early infant death, assuming a rate of 4%, is 83%.

The percent of subjects with preterm birth at < 35 weeks will be determined as the point estimate of the survival function from a staggered entry Kaplan-Meier analysis, to account for gestational age at entry. A two-sided 95% confidence interval (CI) for the relative risk of fetal/early infant loss will be calculated by the Cochran-Mantel-Haenszel method stratifying for gestational age at entry. A doubling of the risk of fetal/early infant loss will be ruled out if the upper bound of the 95% CI is ≤ 2.0.

Division Director's Comments

- *The objectives and key endpoints of the clinical trial were revised in accordance with comments made by the clinical and statistical reviewers.*
- *The inclusion of a clinical endpoint, the neonatal morbidity/mortality index as the key secondary endpoint, analyzed in a hierarchical manner, will address the Subpart H goal of*

extending initial findings based on surrogate endpoints to the demonstration of an actual clinical benefit.

- *The confirmatory clinical trial, as designed, will also address DRUP's concern regarding possible early pregnancy loss in women treated with HPC for prevention of preterm birth.*

7.2 Feasibility of Successfully Conducting the *Confirmatory Study*

The Applicant initially submitted as evidence of feasibility a survey of Obstetricians and Maternal Fetal Medicine specialists that sought to determine their willingness to participate in a placebo-controlled trial of HPC following FDA approval. Participants were also asked whether they anticipated that their Institutional Review Board (IRB) would have concerns about such a study and whether they anticipated that eligible patients would be willing to enroll. Of 325 surveys disseminated, 67 physicians responded (response rate 21%); of these responders, 33 (49%) indicated willingness to participate in such a trial.

Given the low response rate and the relatively small absolute number of physicians willing to participate, DRUP asked the Applicant to provide greater assurance that a post-approval placebo-controlled trial could actually be conducted in the U.S. The Applicant submitted a response on September 3, 2008, following further discussion with key Ob/Gyn opinion leaders and with those physicians who had indicated willingness to participate at the time of the original survey. Among the 33 potential participants, the Applicant obtained letters of continued interest from 11 who were considered to be prominent investigators in academic settings, military bases, or large private practice groups. The Applicant also identified several obstetric researchers at Canadian academic centers who expressed interest in the study.

During the course of this review cycle, the American College of Obstetrics and Gynecology (ACOG) issued a revised Committee Opinion on the Use of Progesterone to Reduce Preterm Birth[2] that included the following statement:

> *"Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes."*

Division Director's Comment

- *Both the primary Medical Reviewer and Medical Team Leader believe that the revised ACOG Committee Opinion on Use of Progesterone to Reduce Preterm Birth has virtually established offering treatment with progesterone to patients with a history of a previous singleton preterm birth as a de facto standard of care. Both reviewers (who are Obstetricians) are concerned that Institutional Review Boards (IRBs) and patients may interpret the ACOG committee opinion as indicating that any remaining questions regarding the efficacy and safety of HPC are not sufficient to justify conducting, or participating in, a placebo-controlled study.*

Because of these concerns regarding the feasibility of the study, the Applicant was informed that DRUP did not believe that letters of intent to participate in a post-approval study, written prior to issuance of the new ACOG opinion, would provide sufficient evidence of the feasibility of the *Confirmatory Study*. Working over a short time interval, the Applicant was able to re-contact

2 ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 419, October 2008.

16 of the 33 original potential investigators. Of these, 4 of 16 indicated that they no longer believed the study could be conducted in the U.S. and would no longer participate in the study. In the process of reassessing the feasibility of successfully conducting the *Confirmatory Study*, the Applicant identified several additional potential U.S. investigators as well as 16 foreign investigators from Canada, Mexico, and Western Europe. In total, the Applicant believes that 55 investigators at 46 sites in 9 countries are likely to participate.

Division Director's Comments

- *Both the primary Medical Reviewer and Medical Team Leader believe that to provide adequate reassurance of feasibility, the Applicant will need to provide a higher level of evidence than a statement of intention by potential investigators to participate in the Confirmatory Study.*
- *Higher level of evidence would include:*
  - *IRB approval for at least 15 investigational sites (including U.S. and non-U.S. sites).*
  - *Enrollment of at least 5% of the total anticipated sample size.*
  - *Enrollment of at least 15 subjects at U.S. study sites*.
- *I concur that a statement of intention by potential investigators to participate in the Confirmatory Study is not adequate to provide sufficient reassurance that the proposed study is likely to be successfully completed. The additional level of documentation recommended by the primary Medical Reviewer and Medical Team Leader is reasonable and does not impose an unreasonable burden on the Applicant.*

7.3 Follow-up Protocol for Children whose Mothers Participated in the *Confirmatory Study*

In the Approvable Letter, the Division had requested additional developmental assessment of children at ages 18-24 months whose mothers had been treated with HPC, including a formal psychometric assessment and an additional assessment by a neurologist for children who screened positive for developmental delay. In response to this request, the Applicant provided an initial protocol for a non-interventional follow-up study of exposed offspring of mothers who had participated in the confirmatory efficacy and safety study. The study will enroll 375 children (250 exposed *in utero* to HPC and 125 exposed to placebo) aged 18-24 months to determine whether there is a difference in the attainment of developmental milestones. Children will be evaluated using the Ages and Stages Questionnaire (ASQ), the same instrument used for screening in Study 17P-FU. Those who score positive for developmental delay in one or more of the five ASQ domains will be referred for further secondary evaluation (e.g., Bayley Scales of Infant and Toddler development, neurological exam, Gross Motor Function Classification System and Modified Checklist for Autism in Toddlers).

Division Director's Comments

- *Final agreement on the design of the follow-up protocol will need to be reached during the next review cycle.*
- *The Approvable Letter of October 20, 2006, also stated that long-term follow-up would likely be required. This request for a long-term safety study was prompted in large part by the worrisome literature report concerning reduced fertility and reproductive performance in male rodents. Given the reassuring results of the new GLP-compliant reproductive toxicology study, the primary Medical Reviewer, the Medical Team Leader, and I feel less*

compelled to require such an adolescent study. If results of concern should be obtained in the infant/toddler follow-up study, DRUP might decide to request a longer-term follow-up study under its FDAAA authorities, based on identification of a new safety signal. However, at this time, neither of the medical reviewers nor I will require that an adolescent study be conducted as a Phase 4 commitment.

7.4 Statistical Reviewer's Assessments

The primary Statistical Reviewer, Lisa Kammerman, PhD, reached the following conclusion, in her review dated October 19, 2006, at the end of the first review cycle for NDA 21-945:

> *"From a statistical perspective, the level of evidence from Study 17P-CT-002 is not sufficient to support the effectiveness of 17P. The primary reason is the absence of a second, confirmatory study. Without a second study, the generalizability of the study results to a larger population cannot be assessed."*

During the current review cycle, there were no new statistical data to review. Dr. Kammerman, however, reviewed the Applicant's initial draft protocol for the requested *Confirmatory Study* and all subsequent protocol revisions. She had significant concerns regarding the original study protocol. These concerns and her recommendations were conveyed to the Applicant. In the Addendum (dated January 14, 2009) to her primary statistical review, she stated the following:

> *"Since completing my statistical review of the applicant's complete response to the approval letter for NDA 21-945, the medical division and I have had numerous discussions with the applicant regarding their draft study protocol: ....*
>
> *This study represents a confirmatory study of the findings from Study 17P-CT-002. As a result of these discussions, the applicant submitted a revised protocol on 12/12/2008. I agree with changes made to the protocol and do not have any additional statistical comments."*

Division Director's Comment

- *Although Dr. Kammerman concurs with the design, endpoints, and analysis plan for the Applicant's proposed Confirmatory Study, she continues to believe that the efficacy findings from the proposed Confirmatory Study should confirm the findings from Study 17P-CT-002 prior to possible approval of HPC for the indication of prevention of preterm birth. She does not concur with DRUP's position that HPC could be approved for prevention of preterm birth under Subpart H. Her concerns regarding possible approval for HPC under Subpart H will be fully addressed by DRUP and ODE III should the Applicant satisfactorily address the deficiencies that are described in the Complete Response Letter of January 23, 2009.*

8. SAFETY (CURRENT SUBMISSION)

No new clinical data were provided in the current submission. Review of the medical literature by the primary Medical Reviewer for new publications since submission of the original NDA did not identify any new safety issues.

Additional safety data that the Applicant will need to obtain as a condition of possible approval under Subpart H for HPC for the prevention of preterm birth in women with a history of a prior singleton spontaneous preterm birth are described in Section 7.1 and Section 7.3.

9. ADVISORY COMMITTEE MEETING (CURRENT SUBMISSION)

As noted earlier, the original Application was presented to the Advisory Committee for Reproductive Health Drugs (ACRHD). It was determine by DRUP that further guidance from the ACRHD was not warranted for the current submission.

10. PEDIATRICS (CURRENT SUBMISSION)

The Applicant requested a full waiver of pediatric studies, and DRUP concurred, as studies would be impossible or highly impractical because there are too few children with the condition to study. The Pediatric Review Committee (PeRC), on December 31, 2008, agreed to a partial waiver for premenarcheal females, and to extrapolate efficacy for postmenarcheal females.

11. OTHER RELEVANT REGULATORY ISSUES (CURRENT SUBMISSION)

No financial disclosure information was included in the present submission (the Complete Response) because no new clinical data were provided.

An audit of the non-clinical multi-generational reproductive toxicology study site was conducted by the Division of Scientific Integrity (DSI). Although some issues were identified, DSI did not believe they warranted a Form 483 and the audit was classified as No Action Indicated (NAI).

12. LABELING (CURRENT SUBMISSION)

The Division of Medication Error Prevention and Analysis (DMEPA) previously evaluated the name, Gestiva, in 2006, and found the name unacceptable due to orthographic and phonetic similarity to the name Sustiva. In response to this rejection, the Applicant provided supportive data to demonstrate that Gestiva would not be distributed via the normal pharmacy distribution channel. Upon evaluation of the aforementioned information, DMEPA reversed their initial decision, and found the proprietary name, Gestiva, acceptable.

Discussions regarding product labeling were conducted, but agreement regarding acceptable labeling was not reached. Product labeling will be addressed during the next review cycle.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT (CURRENT SUBMISSION)

13.1 Regulatory Action

NDA 21-945 (hydroxyprogesterone caproate [HPC] for the proposed indication of "prevention of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth") will not be approved at this time. The basis for this non-Approval (Complete Response) action is that the Applicant has not provided adequate documentation that it will be feasible to conduct and successfully complete the proposed "*Confirmatory Study*" that would be a condition of Approval under Subpart H 21 CFR 314.510.

I concur with the recommendations of the primary Medical Reviewer and the CDTL/Medical Team Leader that adequate documentation of feasibility will include the Applicant completing the following:

1. Obtaining IRB approval at a sufficient number of U.S. and non-U.S. sites so that enrollment of 1,700 subjects into the "*Confirmatory Study*" within a reasonable period of time is likely. No site should enroll more than 15% of the total number of subjects.
2. Enrolling at least 5% of the 1,700 subjects, including at least 15 subjects in the U.S.
3. Agreement (with supporting evidence) to enroll at least 10% of the total sample of 1,700 subjects from U.S. and Canadian sites.

13.2 Rationale for Regulatory Decision

Following a priority review of the original submission for NDA 21-945, which included presentation of the NDA to the Advisory Committee for Reproductive Health Drugs, the Application received an Approvable Action on October 20, 2006. The Application was not approved at that time because of clinical, non-clinical toxicology, and chemistry, manufacturing, and control (CMC) deficiencies. The information provided in the current submission (a Complete Response) adequately addresses the non-clinical toxicology and CMC deficiencies, but does not adequately address the clinical deficiencies.

The public health importance of preterm birth and the lack of an efficacious treatment for preterm labor must be considered in weighing the risk/benefit ratio for a drug proposed for the indication of prevention of recurrent preterm birth. It was concluded by both the clinical and statistical reviewers in the first review cycle that the primary efficacy and safety trial (Study 17P-CT-002) did not meet the general requirements for acceptance of a single adequate and well-controlled trial to provide sufficient evidence of efficacy to support approval of HPC for marketing. The DRUP clinical reviewers and I, based on the totality of the clinical data in the original NDA submission and guidance from the Advisory Committee for Reproductive Health Drugs, concluded that approval of HPC for marketing could be possible under Subpart H 21 CFR 314.510. In the Approvable Letter of October 20, 2006, the Applicant was requested to:

> *"Submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of HPC for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510. If a placebo-controlled trial is determined not to be feasible, provide alternative study design proposals."*

In the present submission, the Applicant has provided an acceptable protocol for the requested *Confirmatory Study* and proposes to initiate and conduct the study post-approval. As stated above in Section 13.1, the clinical reviewers and I believe that to provide adequate reassurance of the feasibility for successfully completing the *Confirmatory Study*, the Applicant will need to provide a higher level of evidence than a statement of intention by potential investigators to participate in the study. The recent Committee Opinion, issued in October 2008 by the American College of Obstetrics and Gynecology (ACOG), on the use of progesterone in women with a history of spontaneous preterm birth has raised the concern of the medical reviewers that successful completion of the proposed placebo-controlled *Confirmatory Study* is not likely to be feasible if the trial is conducted primarily in the U.S. The medical reviewers and I believe that the ACOG opinion has virtually established offering treatment with progesterone to such high-

risk patients as a *de facto* standard of care. Institutional Review Boards (IRBs) and patients may interpret the ACOG Committee Opinion as indicating that any remaining questions regarding the efficacy and safety of hydroxyprogesterone caproate are not sufficient to justify conducting a placebo-controlled study. The information provided in the current application does not provide assurance of IRB approval of, or patient enrollment into, the *Confirmatory Study*. The medical reviewers and I believe that adequate assurance of feasibility can only be addressed by actual initiation of the Confirmatory Study as described in the Complete Response Letter that will be sent to the Applicant on January 23, 2009.

13.3 Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are recommended at this time.

13.4 Recommendation for other Postmarketing Study Commitments

If HPC is eventually approved for the proposed indication, the Applicant will be required to initiate and complete a study that will provide additional information supporting previously obtained data that treatment of mothers with HPC does not have a detrimental effect on early infant/child development (see Section 7.3 of the Memorandum).

The Applicant also will likely be requested (1) to provide data characterizing the pharmacokinetics of HPC and its metabolites in pregnant women at different gestational stages and (2) conduct an *in vitro* study to determine whether HPC induces or alters the activities of CYP1A2, CYP2A6, and CYP2B6.

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/s/

Scott Monroe
1/23/2009 06:45:25 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 505 (b)(2)
Submission Number	21-945
Submission Code	AZ
Letter Date	24 April 2008
Stamp Date	26 April 2008
PDUFA Goal Date	25 January 2009 (with 3 month extension)
Reviewer Name	Barbara Wesley, M.D., M.P.H.
Review Completion Date	23 January 2009
Established Name	17 alpha hydroxyprogesterone caproate injectable
(Proposed) Trade Name	Gestiva
Therapeutic Class	Progestogen
Applicant	Cytyc Corporation
Priority Designation	6-month – Complete Response to Approvable Letter
Formulation	Injectable (Intramuscular - IM)
Dosing Regimen	250 mg (1 mL) weekly from between 16 weeks 0 days and 20 weeks 6 days to 37 weeks of gestation or until delivery
Indication	Prevention of preterm birth
Intended Population	Pregnant women with a history of at least one spontaneous preterm birth

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends a complete response (approvable) action for Gestiva (17α-hydroxyprogesterone caproate [hereafter referred to as 17-HPC, but also known as HPC and 17P]) for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth. This recommendation is based on one multicenter clinical trial that showed statistically significant reductions in preterm birth (PTB) at <35 and < 32 weeks gestation, both surrogate endpoints acknowledged by an Advisory Committee to predict reduction in neonatal mortality and morbidity. However, the findings from this single study alone are not sufficiently persuasive to support approval alone. Additionally, data from the literature do not consistently demonstrate a decrease in PTB when women with a history of previous PTB are treated with 17-HPC.

During the previous review cycle, the Applicant was asked to provide the Agency with protocols to assess the following efficacy and safety parameters:

- Additional data to provide further statistical support for the effectiveness of 17-HPC to reduce the incidence of PTB at <35 and <32 weeks gestational age.
- Safety studies to assess to potential association of 17-HPC with miscarriages/ stillbirths, and long term developmental and safety evaluations of children at age 18-24 months.

In the Action (Approvable) Letter to the original Applicant (Adeza Biomedical) on October 20, 2006, the Agency indicated a willingness to consider Subpart H approval of 17-HPC for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth, since there is currently no other approved drug in the world for this indication. Approval would be contingent on concurrence with the protocol(s) submitted by the Applicant and the Applicant evidence of the feasibility of conducting another randomized, well-controlled trial of 17-HPC in women with a history of previous preterm birth (with a follow-up of their children). No studies of 17-HPC for this specific indication have been completed or undertaken in the U.S. since October 2006. This reviewer believes that these critical additional safety and efficacy studies to investigate 17-HPC to prevent PTB in women with a history of previous PTB would not be done in the U.S. without approval under the Subpart H, 21 CFR 314.510.

This reviewer agrees with the overall design of the draft Protocol (hereafter referred to as the "Confirmatory Study") submitted by the Applicant on January 15, 2009, that is designed to:

1. Confirm one of the previous findings of efficacy in Study 17P-CT-002 (i.e., a reduction in preterm births at < 35^0 weeks of gestation),
2. Obtain further information regarding the effect of treatment with hydroxyprogesterone caproate (HPC) on neonatal morbidity and mortality, and
3. Address the concern regarding early pregnancy loss identified in our Approvable letter of October 20, 2006.

In addition, the Applicant has provided a draft protocol for a follow-up study of offspring up to two years of age in the U.S. and in other countries.

In the October 2008 issue of *Obstetrics and Gynecology*, the American College of Obstetrics and Gynecology (ACOG) published COMMITTEE OPINION #419, *Use of Progesterone to Reduce Preterm Birth*. [1] Despite the lack of additional evidence for efficacy of 17-HPC, or any other progesterone, this document states "*Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes."* This sentence is unambiguous, and has been interpreted as an attempt to create a standard of care. A lack of documentation by the health care provider regarding such counsel for women with this risk of PTB can potentially be considered inadequate, or substandard care. This reviewer is concerned that health care providers and Institutional Review Boards, particularly in the U.S., may be reluctant to conduct randomized, placebo controlled trials of 17-HPC for PTB prevention as a result of this recently published ACOG Committee Opinion.

To provide reassurance that these critical studies are conducted, the following is recommended as a condition for possible approval under Subpart H:

- Obtain IRB approval from approximately 15 research centers (both U.S. and non U.S.) to enroll the target number of 1707 subjects. This recommendation takes into consideration that the applicant may need to make changes (add or subtract sites) at a later time.
- Enroll a minimum of 5% of planned subjects (85 subjects [5% of 1707 subjects]); a minimum of 15 subjects should be enrolled from U.S. sites. No site should ultimately enroll more than 15% of all subjects.
- All sites (U.S. and non U.S.) must use the same pre-defined definitions of neonatal morbidity.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management actions are recommended at this time.

1.2.2 Required Phase 4 Commitments

1. The completion of the "Confirmatory Study" described above. This study will need to be initiated prior to approval but will be completed post-approval under Subpart H.

2. The completion of the a randomized, double blinded, controlled trial to evaluate developmental and safety issues of the offspring from the Confirmatory Study

1.2.3 Other Phase 4 Requests

In consultation with the clinical pharmacologist (Dr. Tran), the following phase 4 postmarketing commitments were agreed upon (see clinical pharmacology review):

1. The sponsor will provide data characterizing the pharmacokinetics (PK) of 17 α-hydroxyprogesterone caproate (17-HPC) and its metabolites in plasma and urine in pregnant women at several periods throughout different gestational stages.
2. The sponsor will conduct an in vitro study using human hepatocytes to determine whether 17-HPC induces or alters the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.

Approximately 450 subjects from the main clinical trial will participate in the population PK substudy. Subjects in the PK population will be stratified based on BMI (≤ 28 and > 28), such that approximately 40% and 60% of subjects are in each BMI category, respectively

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The FDA sent an Action (Approvable) Letter to the original Applicant (Adeza Biomedical) on October 20, 2006 that defined additional information required to obtain approval to market 17-HPC. The following deficiencies and possible remedies were outlined in the letter:

Clinical
"1. Further study is needed to provide confirmatory evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly, or through a well-established surrogate, such as the rate of preterm birth prior to 35 and 32 weeks of gestation.
2. There are insufficient data to evaluate a potential association of hydroxyprogesterone caproate (HPC) with increased risk of early fetal loss (second trimester miscarriage and stillbirth)."

Information needed to address the clinical deficiencies
"1. Submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of HPC for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510. If a placebo-controlled trial is determined not to be feasible, provide alternative study design proposals.
2. Provide a draft protocol to evaluate the potential association of HPC with increased risk of second trimester miscarriage and stillbirth. This could be assessed as a part of the confirmatory efficacy study referred to in Item No. 1 above."

Additional clinical issues that would need to be addressed postmarketing, if the product were to be approved:
"1. Completion of the additional efficacy and safety study(ies) requested above under the description of clinical deficiencies will be required as a condition of an approval under Subpart H 21 CFR 314.510 (Item No. 1 above under clinical deficiencies) or as a formal phase 4 commitment (Item No. 2 above under clinical deficiencies).

2. Long-term post treatment safety data (at least through puberty) from children whose mothers had been treated with HPC is lacking in the NDA. This information is requested and could be obtained through the establishment of a surveillance program (e.g., registry) to evaluate the effects of prenatal exposure in adolescents and young adults. Submit your proposal as to how these data would be obtained.
3. Additional developmental assessment is needed of children at ages 18-24 months whose mothers had been treated with HPC. This assessment could be obtained from the offspring of women enrolled in the confirmatory efficacy study or the safety study addressing early fetal loss. Children who screen positive for developmental delay should have a formal psychometric assessment and an additional assessment by a neurologist."

Complete Response Submitted April 24, 2008

On April 24, 2008, a new Applicant (Cytyc, whose parent company purchased Adeza) submitted a complete response to the October 20, 2006 Approvable letter by providing:

- a draft protocol of a placebo-controlled trial to confirm efficacy and provide additional safety data
- evidence of the feasibility of conducting this additional multicenter, well-controlled trial
- a draft protocol of a randomized controlled trial to assess development of children exposed in utero at ages 18-24 months
- a proposal to evaluate the effects of prenatal exposure of 17-HPC in adolescents
- the interim study report for the nonclinical multigeneration reproductive toxicology study

The proposed confirmatory study as modified during the review process and submitted on January 15, 2009, is a multi-center, randomized, double-blind, placebo-controlled clinical trial in women with a singleton pregnancy, aged 16 years or older, with a history of a previous singleton spontaneous preterm delivery. A total of 1707 subjects will be randomized in a 2:1 ratio to receive either 17-HPC or placebo, respectively. Subjects will receive weekly injections of study drug from randomization (16 weeks-0 days [16^0] through 20 weeks-6 days [20^6] weeks of gestation) until 36^6 weeks of gestation or delivery, whichever occurs first.

The *primary outcome* of this study is to determine if treatment with 17-HPC reduces the rate of preterm birth at $< 35^0$ weeks of gestation in women with a previous singleton spontaneous preterm delivery. The *key secondary outcomes* of this study are to:

- Determine if 17-HPC reduces the rate of neonatal mortality or morbidity, if and only if, the rate of preterm birth $< 35^0$ weeks of gestation is statistically significant (i.e., hierarchical testing approach). Neonatal mortality or morbidity is measured by a composite index comprising:
    - Neonatal death,
    - Grade 3 or 4 intraventricular hemorrhage,
    - Respiratory distress syndrome,
    - Bronchopulmonary dysplasia,
    - Necrotizing enterocolitis,
    - Proven sepsis,

Exclude a doubling of the risk in the 17-HPC group compared to the placebo group of the composite of:

- fetal/early infant death:
    - (defined as spontaneous abortion/miscarriage [delivery from 16^0 through 19^6 weeks of gestation], or
    - death [from minutes after birth until 28 days of life occurring in liveborns born at less than 24 weeks gestation]),
- stillbirth (antepartum or intrapartum death from 20 weeks gestation through term).

Significant differences between the 17-HPC and placebo group in the proportion of subjects who deliver prior to 35° weeks gestation will be determined using a Cochran-Mantel-Haenszel test stratified by gestational age at randomization, where the effective sample sizes for each treatment group will be derived from Greenwood's formula. A hierarchical testing approach will be utilized. Statistical significance will be determined for the primary outcome of preterm birth $<35^0$ weeks of gestation in the intent-to-treat (ITT) population at the 0.05 significance level. If and only if the primary outcome is significant, the secondary outcome of preterm birth the percent of neonates with the neonatal composite index (based on liveborn infants) will be tested for significance at the 0.05 level.

Pharmacokinetic assessments will be made based on a sparse sampling of approximately 450 subjects (approximately 300 active and 150 placebo), stratified according to body mass index (BMI) to analyze the dose-plasma concentration-time relationship of 17-HPC.

Safety
Deaths (miscarriages/pre-viable infants/stillbirths) will be evaluated as a safety outcome to rule out a doubling of the rate of miscarriages/deaths in liveborns less than 24 weeks or stillbirths greater than 20 weeks in subjects who receive 17-HPC versus those who receive placebo.

Stillbirths/fetal deaths/in-utero fetal losses will have a comprehensive work-up, as recommended by the Stillbirth Collaborative Research Network of the National Institute of Child Health and Human Development (NICHD), to investigate the cause of death.

The Applicant proposes to collect and report data on the following complications of pregnancy: gestational diabetes, oligohydramnios, significant antepartum bleeding or hemorrhage, preeclampsia or gestational hypertension, abruption, and chorioamnionitis.

As part of the phase 4 commitments, Cytyc proposes to conduct a follow-up study of children at age 18 to 24 months (when most cases of cerebral palsy and mental retardation can be identified), who were born to mothers who completed the proposed efficacy and safety trial. The objective of this follow-up study will be to determine whether there are differences in the achievement of developmental milestones between children whose mothers received 17-HPC and those whose mothers received placebo. In determining whether developmental differences exist between the two groups, subjects will initially be screened for developmental delay using the Ages and Stages Questionnaire (ASQ). Subjects who test positive for delay in any one of the five ASQ domains will be referred for a secondary assessment of the child's performance in the area(s) for which they screened positive (e.g., further evaluation based on Bayley Scales of

Infant and Toddler Development, neurological exam, Gross Motor Function Classification System, Modified Checklist of Autism in Toddlers).

1.3.2 Efficacy - Original Submission and Literature since April 14, 2006

In support of the original application for marketing approval for 17-HPC (submitted on April 14, 2006) for the prevention of preterm birth, the Applicant (Adeza Biomedical) submitted data from one principal active treatment clinical trial (Study 17P-CT-002; 463 subjects – 310 in the 17-HPC arm), an initial active treatment clinical trial that was terminated prematurely due to recall of the study drug (Study 17P-IF-001; 150 subjects – 65 in the 17-HPC arm) and a follow-up safety analysis (study 17P-FU), all conducted by the NICHD. The principal study was a double-blind, vehicle-controlled trial that randomized subjects 2:1 to 17-HPC or vehicle. Inclusion criteria included pregnant women with a history of a previous spontaneous singleton preterm birth, who were at a gestational age between 16 weeks-0 days (16^0) and 20 weeks-6 days (20^6) at randomization.

The primary efficacy endpoint was percent of births occurring at <37 weeks gestation. Additional endpoints, requested by the FDA, included percent of births at <35 weeks and at <32 weeks gestation, and a composite index of neonatal morbidity and mortality. The composite index of neonatal morbidity/mortality was lower in the 17-HPC group (11.9%, 35/295 infants) than in the vehicle group (17.2%, 26/151 infants) but the between-group difference was not statistically significant.

The efficacy results from study 17P-CT-002 are summarized in Table A.

Table A Proportion of Subjects with Delivery at <37^0, <35^0, <32^0, and <28^0 Weeks

Data Source	17-HPC (N=310)	Vehicle (N=153)	Mean Treatment Differences [A] and 95% Confidence Interval [B]
	%	%	
<37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
<35^0 weeks	21.3	30.7	-9.4% [-18.7%, -0.2%]
<32^0 weeks	11.9	19.6	-7.7% [-16.1.%, -0.3%]
<28^0 weeks	9.4	10.5	-1.1% [-7.4%, 5.2%]
Composite Neonatal Morbidity Score [c]	11.9	17.2	0.1194 (nominal P value)

[A] Chi-square test.

[B] The confidence intervals, based on a t-test, are adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, the final p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

Source: FDA statistical analysis of Applicant's data from Study 17P-CT-002.

c The composite neonatal morbidity measure counted any liveborn infant who experienced death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC. P-values have not been adjusted for multiple comparisons.

Source: Table 11-8, Final Report for Study 17P-CT-002.

The strength of the efficacy data relies on statistically significant reductions of PTB at <37, < 35 and < 32 weeks gestation. The surrogate endpoints of reductions of PTB at < 35 and

< 32 weeks were thought by the Advisory Committee to predict a reduction in neonatal mortality and morbidity. The Advisory Committee was primarily supportive of approving this drug, with the stipulation that another confirmatory clinical trial should be conducted for further demonstration of safety and efficacy. The Committee was willing to approve on the basis of a single clinical trial primarily because there are no other available therapies for this major public health problem.

The major weakness of the original Application in demonstrating efficacy was that it relied for evidence of effectiveness on a single "multicenter" study which did not include a population that was representative of the United States population:

- The percentage of black (African American) subjects in this study was 59%; during the same time frame, the percentage of blacks (African Americans) in the U.S. was 12%. Although the odds ratio of PTB in black couples is 2.4% greater than white couples (Simhan 2008 [2]), and it is prudent to include a disproportionately higher number of blacks (African Americans) in this type of study, this study still does not represent the spectrum of PTB in the U.S.

Other limitations of the study included:

- There was imbalance in the contribution of the centers. One center (University of Alabama) out of 19 centers in the MFMU Network contributed almost 30% of all subjects. The reduction in PTB < 32 weeks at the University of Alabama center was much more pronounced than in all other centers combined (see Table 3) and appears to have driven the significance of the results at <32 weeks.
- The preterm birth rate of 54.9% in the vehicle arm was considerably greater than the background rate of 36% used to power this study. The rate of 54.9% preterm birth, is also considerably higher that of the control arm (36%) in another Maternal-Fetal-Medicine Network study, the Home Activity Uterine Monitoring study. The PTB rate of 37.1% in the 17-HPC arm is no lower than the PTB rate of 36% in the control arm of the Home Activity Uterine Monitoring study.
- The efficacy results of prevention of PTB at < 35 weeks and < 32 weeks (all centers), while statistically significant, were not statistically persuasive, with the upper bound of the confidence interval around the difference between 17-HPC and placebo approaching 0: -9.4% [-18.7%, -0.2%] reduction in births less than 35 weeks; -7.7% [-16.1%, -0.3%] reduction in births at less than 32 weeks.

The results of some studies in the literature provide *conflicting support for the effectiveness of 17-HPC* for prevention of PTB (Thornton, 2007 [3] ; Denny, 2008 [4] ; Smith, 2009 [5] ; Basaran 2007 [6]). Selected publications (see section 6.1.4 for more details) since February 2006 include the following:

- One placebo-controlled study of 17-HPC to prevent PTB in women with twin gestations who had a previous PTB was completed and published by the NICHD Maternal-Fetal Medicine Units (MFMU) Network. *It did not demonstrate effectiveness* (Rouse 2007 [7]); however, further studies are underway to determine if a higher dose is required in multiple gestations.
- Two studies were published based on other sources of progesterone (vaginal progesterone; Prochieve®); efficacy was demonstrated when the at-risk population was defined by *short*

cervix as a risk factor but not when risk was defined by previous PTB (Fonseca 2007 [8] ;O'Brien 2007 [9]).

1.3.3 Safety - Original Submission and Literature since April 14, 2006

Listed below are the overall safety results from study 17-CT-002:

- There were no definitive significant safety signals identified.
- There was a trend toward an increased risk of miscarriage and stillbirths in the 17-HPC treatment arm, and a trend toward a decrease in neonatal death, with no overall net survival benefit.

Table B Miscarriages, Stillbirths, and Neonatal Deaths

Pregnancy Outcome	17-HPC N=306 n (%)	Placebo N=153 n (%)	Nominal P-value [A]
Miscarriages <20 weeks gestation	5 (1.6)	0	0.1746
Stillbirth	6 (2.0)	2 (1.3)	0.7245
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.1159
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.6887**

[A] No adjustment for multiple comparisons.
Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

- In studies 17P-CT-002 and 17P-IF-001, there was a suggestion that 17-HPC may impair glucose tolerance; this warrants further study. Also based on trends in these studies, there is reason to further study the effects of 17-HPC on amniotic fluid levels and preeclampsia.
- Injection site pain, swelling and pruritus were the most common adverse reactions (ARs) and reasons for discontinuation in study 17-CT-002.

Since 2006, several publications have shed some further light on safety of 17-HPC in pregnant women:

- **Miscarriages/Stillbirths**
  - In one randomized placebo-controlled trial conducted by the NICHD MFMU Network [10], in which 17-HPC was initiated between 16^0 and 20^6 weeks, there was no specific trend in miscarriage or stillbirth comparing 17-HPC to placebo.
  - In one retrospective review of a database, the fetal loss rate at <24 weeks was comparable to controls, but there was an increased rate of miscarriage in the 17-HPC arm at <20 weeks of gestation (Gonzalez-Quintero 2007a [11]).
- **Diabetes in Pregnancy**
  - In one retrospective review of a database, 17-HPC-exposed subjects had an increased incidence of gestational diabetes compared with placebo (Rebarber 2007a [12]).

Regarding the NICHD MFMU Network follow-up study 17P-FU:

- There were no signals of developmental delay in the limited follow-up study of children; however, this study was an "ad hoc" addition to the principal study and as such, had some deficiencies, e.g., less than optimum recruitment into the study and lack of neurologic examination in children who screened positive, etc.

In an AERS search on 17-alpha hydroxyprogesterone caproate by the FDA, six new reports were submitted since October 2006; three were related to preterm labor, therefore not thought to be drug-related and no definitive conclusions can be drawn from the single report each of syncope and depression in the mother, and congenital heart defect in the infant.

Finally, of significant concern is the fact that several national surveys have indicated that a large number of obstetricians currently treat pregnant women with compounded 17-HPC, which is not available as an FDA-regulated, Good Manufacturing Process (GMP)-produced product.

1.3.4 Dosing Regimen and Administration

The dosing regimen was a weekly intramuscular injection of 250 mg of 17-HPC beginning at 16^0 weeks to 20^6 weeks gestation and continued through 36^6 weeks gestation or birth. This dosing regimen appears to have been based on previously reported studies, most notably that of Johnson et al (see table 6). This dosing regimen has been used for off-label indications for several decades. Dose ranging studies were not submitted as part of this NDA; however the Applicant is planning to conduct pharmacokinetic (PK) studies.

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies were submitted as part of the NDA. Only a small number of subjects received concomitant medications that were likely to either increase or decrease the metabolism of 17-HPC. Consequently, no conclusions about drug interactions can be made.

1.3.6 Special Populations

Women and Children. All subjects in the studies were pregnant women. 17-HPC is to be used only in this population (including pregnant adolescents).

Renal and Hepatic Impairment. Subjects with renal or hepatic compromise were excluded from the clinical trials. Because the use of 17-HPC may not be appropriate to prevent preterm birth in this population, no studies in pregnant women with significant renal or hepatic impairment are warranted.

Racial and Age Differences in Efficacy and Safety. Among the racial/ethnically diverse reproductive age female population studied, no significant differences in safety or efficacy were observed, with the exception of a lower percentage of injection site reactions in Black subjects. The subjects in Study 17P-CT-002 were approximately 60% Black/African American, 26% White/Caucasian, 14% Hispanic, and 1% Other.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Cytyc Inc. has submitted a complete response to New Drug Application (NDA) 21-945 for 17α-hydroxyprogesterone caproate (17-HPC) injection for the proposed indication:

> "Prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth"

Preterm birth is defined as a birth prior to 37 weeks 0 days (37^0) gestational age.

The proposed dosing regimen is a weekly intramuscular injection of 250 mg of 17-HPC in 1 mL castor oil with 46% benzyl benzoate and 2% benzyl alcohol, beginning at 16 weeks 0 days (16^0) to 20 weeks 6 days (20^6) weeks gestation and used through 36^6 weeks gestation or birth.

GESTIVA is a clear, yellow, sterile, non-pyrogenic solution for intramuscular injection. Each 5 mL vial contains 17 α-hydroxyprogesterone caproate for injection USP, 250 mg/mL (25% w/v), in castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

Castor Oil Issues

Rare post-marketing reports from outside the U.S. describe an immediate post-injection reaction characterized by transient symptoms that include urge to cough, coughing spells, dyspnea and respiratory distress, occurring immediately after the deep gluteal injection of 4 mL of an oily solution (castor oil) of testosterone undecanoate. It is postulated that these reactions are due to the phenomenon of pulmonary oil microembolism (POME) that can occur following direct vascular or lymphovascular delivery of oil-based preparations, which then reach the lung as the first "filtering" organ from venous return circulation and right heart output. POME has not been described in preparations that contain less than 4 mL of castor oil, although cough reactions have rarely occurred with marketed oily depot hormone preparations having a volume of 1 mL, or 2mL.

Medical Officer's Comments:

- *There is virtually no risk of POME with the volume to be delivered for Gestiva; however, the Applicant has agreed to monitor the subjects for coughing and shortness of breath post injection.*

2.2 Currently Available Treatment for Indications

Currently there is no drug product approved in the United States for prevention of preterm birth; however, 17-HPC is being compounded by pharmacists and is being used widely for prevention of preterm birth in women at high risk. The medical need for an approved drug product for prevention of preterm birth is particularly acute because there also are no approved drug products currently marketed in the United States for the treatment of preterm labor. Although several

drug products with tocolytic properties (i.e., stopping uterine contractions) are used off-label for treatment of preterm labor, randomized controlled trials have failed to demonstrate that these drugs improve perinatal outcomes.

Use of Compounded 17-HPC

17α-hydroxyprogesterone caproate is being compounded by pharmacists and is being used widely for prevention of preterm birth in women in the U.S. In addition, clinicians are also using other forms of progesterone, approved for other indications, to prevent preterm birth.

Two mail surveys were sent to all board certified Maternal-Fetal Medicine (MFM) sub-specialists in the United States to evaluate the use "progesterone" to prevent preterm birth: The objective of the first study (Ness 2003 [13]) was to determine the current prescription of progesterone to prevent preterm birth (PTB) among board-certified maternal-fetal medicine (MFM) specialists in the United States. A survey was sent to examine their prescription of and attitudes regarding progesterone (several preparations) to prevent PTB 6 months following publication of the National Institute for Child Health and Human Development trial (study 17P-CT-002). Of 1,264 questionnaires sent, 526 were returned (response rate, 42%). One hundred ninety-eight (38%) respondents prescribed progesterone, and 324 (62%) did not. *Most non-prescribers were awaiting more data and were more concerned than prescribers about long-term effects ($p < 0.0001$). Twenty percent of prescribers prescribed progesterone for women with current signs or symptoms of preterm labor.*

The purpose of a follow-up study (Bailit 2007 [14]) was to determine whether current attitudes regarding the use of progesterone to prevent preterm birth have changed since their last survey in 2003. They mailed a 20 question survey to 1264 board certified Maternal-Fetal Medicine specialists in the United States between February and March of 2005 asking about their use and attitudes regarding progesterone to prevent preterm birth. Five hundred and seventy-two surveys were returned (response rate of 45%). In 2005, 67% of respondents used progesterone to prevent SPTB, compared to 38% in 2003 ($P < .001$). *Among users, 38% recommended progesterone for indications other than previous SPTB. Users were more concerned about lack of insurance coverage compared to nonusers but nonusers were more concerned about safety, efficacy, need for more data, and long-term neonatal effects.*

The use of 17-HPC (presumably obtained from compounding pharmacies) in a community setting was explored retrospectively using the Matria Healthcare database (Rittenberg 2007a [15]). Data were reviewed retrospectively from patients enrolled for outpatient administration of weekly 17-HPC injections and nursing assessments between April 2004 and January 2006 at centers in Charleston, SC and Marietta, GA. The objective of the study was to describe clinical characteristics and pregnancy outcomes of women in a community setting who were prescribed 17-HPC for prevention of preterm delivery. Of 2,159 women prescribed 17-HPC, pregnancy outcome data were available for 1,979 (91.7%). Of the 1,517 women with singleton pregnancy and prior preterm delivery (NICHD study criteria), 56.2% initiated 17-HPC therapy prior to 21 weeks and 43.8% at or after 21 weeks of gestation; they received an average of 12.6 injections, with 2.4% discontinuing after one injection. *Approximately one-fourth (24.0%) of all the women with outcome data (n=1,979) electively discontinued weekly 17-HPC injections prior to 34 weeks gestation or the occurrence of preterm delivery*. Specific discontinuation rates were not

available for the 1,517 women with singleton pregnancy and prior preterm delivery. The overall rate of recurrent spontaneous preterm delivery for the 1,517 women was 36.2% for <37 weeks, 14.8% for <35 weeks, and 6.0% for <32 weeks. No control group was used for comparison. The review of patients treated with 17-HPC at these two medical centers suggests that in current clinical practice, *one-third of patients receiving 17-HPC may not meet the accepted indications*. In addition, *early initiation and adherence to completion of therapy may be a greater issue than observed during clinical trials*. No maternal or fetal safety concerns were reported as part of this retrospective study.

In a community setting, Rittenberg and colleagues studied the outcome of women receiving 17-HPC who were hospitalized for preterm labor at <34 weeks gestation and then received weekly or daily assessments (83 matched-pairs) (Rittenberg 2007c [16]). The women who received *daily perinatal nursing surveillance (including uterine activity monitoring) compared to weekly outpatient prenatal assessments, delivered on average at 35.2 weeks compared to 33.9 weeks gestation (p=0.027) and had significantly fewer births at <32 weeks (9.6% vs. 24.1%; p=0.017).* No safety measures or incidence of neonatal morbidities were reported.

Medical Officer's Comments:

- *These data illustrate that both women and providers are desperate for treatments to prevent the extraordinary public health problem of preterm birth, despite concerns about insufficient data and patient-perceived significant safety concerns.*
- *Providers have been willing to treat women who do not meet the "accepted indication" – women with a previous preterm birth. Approval with well-defined instructions for use that will be provided in the 17-HPC package labeling may help to address this problem.*
- *These data support other studies that demonstrate that intensive nursing support can reduce preterm birth.*

2.3 Availability of Proposed Active Ingredient in the United States

In 1956, the FDA approved the marketing of hydroxyprogesterone caproate (NDA 10-347, Delalutin), for the treatment in pregnant women of habitual and recurrent abortion, threatened abortion, and post-partum "after pains," and for the following indications in non-pregnant women: amenorrhea, dysfunctional uterine bleeding, disturbances of menstrual cycle, deficiency syndromes, dysmenorrhea, premenstrual tension, and cyclomastopathies. In addition, the drug was indicated for the production of secretory endometrium and desquamation and for the suppression of gonadotropic hormone production and ovulation. This approval was based largely on review of safety, in that it occurred prior to the FDA Drug Amendment of 1962, which required that drugs must have substantial evidence of efficacy in addition to evidence of safety in adequate and well-controlled trials.

In 1972, the FDA approved the marketing of 17-HPC for an indication of advanced adenocarcinoma of the uterine corpus (stage III or IV) (NDA 16-911, Delalutin).

In 2000, the FDA withdrew approval for Delalutin. This action was taken at the request of the holder of the NDA because the holder was no longer marketing the drug. The action was not

taken because of safety or efficacy concerns. 17-HPC is currently being compounded by pharmacists in the United States. See Section 2.2.

2.4 Important Issues with Pharmacologically Related Products

There are no therapeutic equivalents for this drug.

2.5 Pre-submission Regulatory Activity

The use of 17-HPC for the prevention of recurrent preterm birth was investigated by the (NICHD) (MFMU) Network, which at that time consisted of 19 university-based clinical centers in the U.S. After this data was published in the New England Journal of Medicine (Meis et al., 2003 [17]), the then-Applicant, Adeza Biomedical, met with the Division of Reproductive and Urologic Products (hereafter referred to as DRUP or the Division) to discuss the possibility of using this data as the basis for an NDA for the indication of 17-HPC for prevention of preterm birth. This clinical trial, however, was not originally intended for drug approval purposes.

The Division conveyed several recommendations and concerns to the Applicant during this and subsequent meetings. These included the following:

- A major concern was the lack of follow-up data, beyond the period of initial hospital assessment, of babies of mothers who had received 17-HPC for the prevention of preterm birth. The Division requested that the Applicant obtain follow-up data on children through at least 2 years of age.
- A second major concern related to the drug product(s) used during the trial. The Applicant was informed that complete chemistry, manufacturing and control (CMC) information would need to be provided about the drug product, including its purity and potency. The Applicant would need to provide information that the drug product used in the NIH sponsored clinical trial and the to-be-marketed formulation would be identical.
- The Division had some concerns about endpoints of Study 17P-CT-002 and the adequacy of these endpoints to support approval of a new drug product for marketing in the U.S, particularly since the NDA supporting the safety and effectiveness of 17-HPC would be based primarily on the outcome of a single clinical trial. These concerns included:
  - The lack of any suggestion of improvement in overall mortality, and only a suggestion of an improvement in overall morbidity in the 17-HPC treated subjects compared to the placebo treated subjects.
  - Clinical Trial 17P-CT-002 did not show a statistically robust effect for reducing the number of births at gestational ages <35 and <32 weeks, when infant morbidity/mortality is a much greater clinical problem in the U.S. The Division, however, recognized that the trial was not powered for these endpoints.
  - The primary endpoint of Clinical Trial 17P-CT-002 was a surrogate for pregnancy outcome (neonatal/infant morbidity and mortality). The Division indicated that its review would also consider what it believed to be the most important outcomes (overall survival of fetuses/infants and a significant reduction in serious morbidities

from the time of enrollment rather than only an increase in gestational age, without other accompanying clinical benefits).

- Normally, either two adequate and well-controlled studies or a single study with a robust and compelling outcome and strong supporting data would be required to support approval of a new drug product. There was a possibility that the data from Trial 17P-CT-002 would not be sufficient to demonstrate that 17-HPC is safe and effective for the prevention of preterm birth.

2.5.1 Studies to Support NDA 21-945 (Submitted April 14, 2006)

The results of the NICHD research (Meis et al, cited above) formed the clinical basis of the New Drug Application (NDA) 21-945, which was submitted to the Food and Drug Administration (FDA) on 14 April 2006.

In support of their application for the use of 17-HPC for the prevention of preterm birth, the then-Applicant (Adeza Biomedical) submitted data from two active treatment clinical trials (study 17P-IF-001 and study 17P-CT-002) and a follow-up safety study (study 17P-FU).

Initial Formulation Study (Study 17P-IF-001). This study began in February 1998, but treatment was terminated in March 1999 because the active study drug (17-HPC) was recalled by its manufacturer, under the direction of the FDA, due to violations of manufacturing practices potentially affecting the potency of the drug. At the time of termination, only 150 of the proposed 500 subjects had been randomized, and no data analysis had been done. Eighty six (86) subjects completed the treatment regimen before the study was stopped: 57 of the 17-HPC subjects and 29 of the vehicle subjects. The study drug used in this prematurely terminated study is referred to as the Initial Formulation (IF). Information from this study was considered to be of limited value in supporting either the safety or efficacy of 17-HPC.

Principal Safety and Efficacy Trial (Study 17P-CT-002). The principal study was published in the New England Journal of Medicine (Meis 2003) was a double- blind, vehicle-controlled trial that randomized subjects 2:1 to 17-HPC or vehicle. Inclusion criteria were: pregnant women with a history of a previous spontaneous singleton preterm birth, who were at a gestational age between 16 weeks-0 days (16^0) and 20 weeks-6 days (20^6) at randomization. The main exclusion criteria included a known major anomaly, prior progesterone or heparin treatment in the current pregnancy, a history of thromboembolic disease and maternal medical/obstetrical complications, hypertension requiring medication, or a seizure disorder. Study medications were 17-HPC (250 mg/mL) in castor oil or vehicle. The dosing regime was a 250 mg weekly injection of 17-HPC, or 1 mL vehicle, beginning on the day of randomization through 36^6 weeks gestation, or delivery, whichever occurred first.

The primary efficacy endpoint was percent of births at <37 weeks gestation. Additional endpoints, requested by the FDA, included percent births <35 weeks and <32 weeks gestation, and a composite index of neonatal morbidity/mortality. The composite was based on the number of infants who experienced any one of the following: death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis or necrotizing enterocolitis (NEC). This study was designed to enroll 500

subjects; however, because the pre-specified stopping criterion for efficacy was attained at an interim analysis, only 463 subjects were randomized (2:1 to 17-HPC vs. vehicle) and treated with study medication: 310 in the 17-HPC arm and 153 in the vehicle arm. Twenty seven (27) subjects withdrew from treatment in the 17-HPC arm vs. 14 in the vehicle arm, but remained in the study for determination of outcome. In the 17-HPC arm, seven withdrew due to an adverse event, compared to three in the vehicle arm. Four subjects were lost to follow-up, all in the 17-HPC arm.

The number of subjects enrolled at each of the 19 study centers is listed in Table 1
Almost 30% of the subjects (126 of 463) were enrolled at a single center – University of Alabama.

Table 1 Enrollment of Subjects by Study Center

Center #	Name	# Enrolled
8	**University of Alabama**	**126**
4	University of Tennessee	45
20	University of Utah	43
18	University of Texas Southwestern	39
2	University of Pittsburgh	36
15	Ohio State University	28
9	Wayne State University	24
21	Thomas Jefferson University	24
13	Wake Forest University	22
11	University of Cincinnati	13
19	University of Texas San Antonio	13
17	University of Miami	11
23	Columbia University	11
14	University of Chicago	7
25	Case Western University	6
22	Brown University	5
26	University of Texas Houston	4
27	University of North Carolina, Chapel Hill	4
28	Northwestern University	2

Source: Table 1, 17P-CT-002 Final Study Report.

Medical Officer's Comment:

- *The disproportionately high enrollment at the University of Alabama site is of concern; the disproportionately small enrollment numbers at several sites is also of concern. This disparity in enrollment numbers negates the balance one expects in a multicenter trial (see efficacy discussion below).*

Follow-up Safety Study (Study 17P-FU). This was a safety study of children whose mothers had participated in Study 17P-CT-002 (Northen 2007 [18]). The study collected data with a validated child development instrument (the Ages and Stages Questionnaire [ASQ]), a survey questionnaire concerning the health and development of the child, and a physical examination.

All children were at least two years of age at the time of the follow-up assessments. The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received weekly intramuscular injections of 17-HPC compared with vehicle in Study 17P-CT-002. Two hundred seventy eight (278) children were enrolled: 194 from the 17-HPC arm, and 84 from the vehicle arm of Study 17P-CT-002.

Efficacy

Study 17P-CT-002. The primary efficacy endpoint was the percent of preterm births (PTBs) <37 weeks gestation and the analysis was based on the intent-to-treat (ITT) population, all subjects who received at least one dose of study medication (see Table 2). Of the 310 subjects treated with 17-HPC, 115 (37.1%) delivered prematurely. Of the 153 subjects treated with vehicle, 84 (54.9%) delivered prematurely. There was a 17.8% reduction (95% CI:-28%, -7%) in preterm births <37 weeks gestation. The reduction in preterm birth < 37 weeks was independent of race, number of qualifying preterm births, and gestational age of the qualifying preterm birth. The percentages of PTB in the 17-HPC arm at <35 and <32 weeks were also statistically significantly lower than those in the vehicle arm. The point estimates of the differences were -9.4% (95% CI:-18.7%, -0,2%) at <35 weeks and -7.7% (95% CI:-16.1%, -0.3%) at <32 weeks.

Table 2 Proportion of Subjects with Delivery at <37^0, <35^0, <32^0, and <28^0 Weeks

Data Source	17-HPC (N=310)	Vehicle (N=153)	Mean Treatment Differences [A] and 95% Confidence Interval [B]
	%	%	
<37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
<35^0 weeks	21.3	30.7	-9.4% [-18.7%, -0.2%]
<32^0 weeks	11.9	19.6	-7.7% [-16.1.%, -0.3%]
<28^0 weeks	9.4	10.5	-1.1% [-7.4%, 5.2%]
Composite Neonatal Morbidity Score [c]	11.9	17.2	0.1194 (nominal P value)

[A] Chi-square test.

[B] The confidence intervals, based on a t-test, are adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, the final p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

Source: FDA statistical analysis of Applicant's data from Study 17P-CT-002.

c The composite neonatal morbidity measure counted any liveborn infant who experienced death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC. P-values have not been adjusted for multiple comparisons.

Source: Table 11-8, Final Report for Study 17P-CT-002.

There was consistency in the reduction of PTB across centers at < 37 weeks and < 35 weeks gestation; however, at < 32 weeks there was a greater reduction of PTB in the 17-HPC arm relative to vehicle at the University of Alabama compared to all other sites combined (see Table 3

Medical Officer's Comments:

- *This reduction in the <32 week delivery rate at the University of Alabama appears to reflect both a lower delivery rate in 17-HPC subjects and a higher delivery rate in the vehicle subjects at <32 weeks as compared to the other centers involved in the trial.*
- *The preterm birth rate of 54.9% in the vehicle arm was considerably greater than the background rate of 36% used to power this study. The rate of 54.9% preterm birth, is also considerably higher that of the control arm (36%) in another MFMU study, the Home Activity Uterine Monitoring study.*
- *The PTB rate of 37.1% in 17-HPC arm is no lower than the PTB rate of 36% in the control arm of the Home Activity Uterine Monitoring study.*

Table 3 Effect of Center on Proportion of Preterm Births at Weeks <37, <35, and <32

	University of Alabama			All Other Centers Combined			All Centers		
Data Source	17-HPC[a] (n=86) %	Vehicle (n=40) %	% PTB decrease	17-HPC[a] (n=224) %	Vehicle (n=113) %	% PTB decrease	17-HPC[a] (n=310) %	Vehicle (n=153) %	% PTB decrease
<37 weeks	26.7	45.0	-18.3 %	41.1	58.4	-17.3 %	37.1	54.9	-17.8 %
<35 weeks	17.4	27.5	-10.1 %	22.8	31.9	-9.1 %	21.3	30.7	-9.4 %
<32 weeks	10.5	25.0	-14.5 %	12.5	17.7	-5.2 %	11.9	19.6	-7.7 %

Source: Response to FDA Question 1, 10/6/06

[a] Four 17-HPC-treated patients were lossed-to-follow-up. They are counted as deliveries at their gestational ages at time of last contact (18.6, 22.0, 34.4 and 36.6 weeks).

Medical Officer's Comment:

- *The efficacy results of prevention of PTB at < 35 weeks and < 32 weeks (all centers) is not statistically persuasive, with the upper bound of the confidence interval around the difference between 17-HPC and placebo approaching 0: 9.4% [-18.7%, -0.2%] reduction in births less than 35 weeks; -7.7% [-16.1.%, -0.3%] reduction in births at less than 32 weeks.*
- *The disproportionate reduction in PTB at the Alabama site (especially at <32 weeks) heavily drives the statistical significance of the reduction of PTB < 32 weeks when all centers are combined.*

The percentage of Black subjects in Study 17P-CT-002 was 59% in both groups. 17-HPC, compared to vehicle, reduced the rate of preterm birth of <37 weeks gestation for both the Black (36.1% vs. 52.2%) and the Non-Black (38.6% vs. 58.7%) populations.

Medical Officer's Comment:

- *Although the percent reduction of PTB was comparable in both black and non-black subjects, the percentage of black subjects (59%) in Study 17P-CT-002 was substantially greater than the percentage of blacks in the general U.S. population (approximately 12%). This further reduces the generalizability of the results.*

The proportion of infants with a birthweight < 2500 g, corresponding approximately to ≤ 37 weeks gestational age, was statistically significantly lower in the 17-HPC arm (27.2%, [82/301] vs. 41.1% [62/151] in the vehicle arm). The number with a birthweight < 1500 g, corresponding approximately to ≤ 32 weeks gestation, was numerically, but not statistically significantly lower in the 17-HPC arm (8.6% vs. 13.9% in the vehicle arm). The prolongation of pregnancy, defined as the time from randomization to delivery or date last pregnant, was numerically longer, by a mean of six days, in the 17-HPC group compared to the vehicle group. The mean gestational age at delivery was one week greater in the 17-HPC group compared to the vehicle group (36.2 vs. 35.2 weeks, p=0.031).

Neonatal mortality was numerically lower in the 17-HPC group, but the between-group difference was not statistically significant (2.6% vs. 5.9%). The composite index of neonatal morbidity was lower in the 17-HPC group (11.9%, 35/295 infants) than in the vehicle group (17.2%, 26/151 infants) but the between-group difference was not statistically significant.

The strength of the efficacy data relies on statistically significant reductions of PTBs at <37, < 35 and < 32 weeks gestation. The surrogate endpoints of reductions of PTBs at < 35 and < 32 weeks were thought by the Advisory Committee to predict a reduction in neonatal mortality and morbidity. The results of studies in the literature provide further support for the effectiveness of 17-HPC for prevention of PTB; however, the small sizes and variable entry criteria for these studies limit the strength of their findings.

Medical Officer's Comment:
The major weaknesses of the original application were:

- *It relied on a single multicenter study for evidence of effectiveness.*
- *There was imbalance in the weighted contribution of the centers.*
- *There was a large imbalance in the weighted contribution of racial/ethnic groups when compared the general U.S. population.*
- *The statistical significance of reduction of PTB at <32 weeks was not persuasive because the efficacy results at this gestational age may have been primarily driven by the University of Alabama site.*

Safety

Study 17P-CT-002. There were no maternal deaths. Eleven subjects discontinued because of an adverse event. Seven subjects were in the 17-HPC arm: three with urticaria, two with injection site pain or swelling, one with arthralgia, and one with weight gain. Four subjects were in the vehicle arm: two with pruritus, one with urticaria, and one with injection site pain. The most common serious adverse events (SAEs) were congenital anomalies. The number and type of these anomalies appeared evenly distributed over the two treatment arms. There were three reports of a SAE in the mothers, all in the 17-HPC arm; none were thought by the investigators

to be related to the study drug. The SAEs were: one subject with a pulmonary embolus 8 days after delivery; a case of cellulitis at the study medication site; and one case that included postpartum hemorrhage, respiratory distress and endometritis.

The most common adverse events (and the percentage of subjects reporting them) in the 17-HPC group were injection site pain (34.8%), injection site swelling (17.1%), urticaria (12.3%), pruritus (7.7%), injection site pruritus (5.8%), nausea (5.8%), and contusion (5.5%). The most common adverse events (and the percentage of subjects reporting them) in the vehicle group were injection site pain (32.7%), urticaria (11.1%), contusion (9.2%), injection site swelling (7.8%), pruritus (5.9%), and neonatal death (5.9%).

Table 4 lists the numbers of miscarriages, stillbirths and neonatal deaths in each group. The observed reduction in neonatal deaths was offset by an increase in second trimester miscarriages and stillbirths in the 17-HPC group. Thus, when considering overall mortality, there was no net survival benefit.

Table 4 Miscarriages, Stillbirths, and Neonatal Deaths (Study 17P-CT-002)

Pregnancy Outcome	17-HPC N=306 n (%)	Vehicle N=153 n (%)	Nominal P-value
Miscarriages <20 weeks gestation	5 (1.6)	0	0.17
Stillbirth	6 (2.0)	2 (1.3)	0.72
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.12
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.69**

[A] No adjustment for multiple comparisons.
Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

Of nine complications of pregnancy reported by the Applicant (in both the principal study 17P-CT-002 and the initial formulation study 17P-IF-001), this reviewer identified three where the percentage of affected subjects was numerically greater in the 17-HPC arm. The pregnancy complications were gestational diabetes, oligohydramnios, and preeclampsia (see Table 5).

Table 5 Selected Pregnancy Complications

Pregnancy Complication	Study	17-HPC N (%)	Vehicle N (%)
Gestational Diabetes	CT- 002	17 (5.6)	7 (4.6)
	IF- 001	8 (8.6)	0 (0.0)
Oligohydramnios	CT- 002	11 (3.6)	2 (1.3)
	IF- 001	2 (2.2)	1 (1.9)
Preeclampsia	CT- 002	27 (8.8)	7 (4.6)
	IF- 001	6 (6.5)	2 (3.8)

Source: Table 12-3 Final Report for Study 17-CT-002 and Study 17-IF 001

Brief Summary of Safety Findings from Study 17P-IF-001. There was no increase in the incidence of miscarriage or stillbirth rate in the 17-HPC treated subjects. There was only one case of miscarriage in each treatment arm. In terms of stillbirths, there were two cases in the

vehicle arm compared to one case in the 17-HPC arm. There were two neonatal deaths in the 17-HPC arm, and none in the vehicle arm. The percentages of subjects with gestational diabetes and preeclampsia were higher in the 17-HPC treated subjects.

Study 17P-FU. There was no difference between the 17-HPC and vehicle groups in the percentage of children who scored below the cutoff for at least one developmental area of the primary endpoint of the ASQ. The percentages of children who scored below the ASQ cutoff in each of the five individual developmental areas were similar in the 17-HPC and vehicle groups. Developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age-mates in physical, mental, social/emotional, or speech development, was reported for a comparable percentage in the 17-HPC and vehicle groups.

Medical Officer's Comment:

- *This ad hoc study was able to reach almost 80% of offspring; however, major weaknesses include:*
    - *No examination by a neurologist or developmental pediatrician*
    - *No follow-up confirmatory studies of children with a positive ASQ score*

Safety Conclusions:

- *There are no definitive safety issues that have been identified.*
- *There is a suggestion of an increase in miscarriages and stillbirths in 17-HPC treated subjects, the most concerning safety signal.*
- *There is also a suggestion that 17-HPC may impair maternal glucose tolerance, requiring further study; there is reason to study further the effects of 17-HPC on amniotic fluid levels and preeclampsia.*
- *Injection site pain, swelling and pruritus were the most common adverse events (AEs) and reasons for discontinuation.*
- *There were no signals of developmental delay in the limited follow-up study of children; however, this study was an "ad hoc" addition to the principal study and as such, had some deficiencies; e.g., less than complete recruitment into the study and lack of neurologic examination in children who screened positive.*

2.5.2 Advisory Committee (August 29, 2006)

A meeting of the Advisory Committee for Reproductive Health Drugs (ACRHD) was held in August 2006 to review data submitted in the NDA that supported the use of 17-HPC for the prevention of recurrent preterm birth.

The major issues that the FDA asked the ACRHD to consider included:

1. Adequacy of Clinical Data to Support the Effectiveness of 17-HPC

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 potentially serious outcome, and confirmation of the result in a second trial would be logistically impossible or ethically unacceptable. The Applicant (Adeza Biomedical) was seeking approval for 17-HPC 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 < 37 weeks gestation).

Described below is the list of issues/questions relevant to this issue that the FDA posed to the AC and the subsequent AC vote:

Question 1

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

Medical Officer's Comments:

- *Study 17P-CT-002 demonstrated a statistically significant reduction in the primary endpoint of preterm births prior to 37^0 weeks gestation. However, the reduction in preterm births prior to 35^0 weeks and prior to 32^0 weeks gestation, better surrogates for significant neonatal morbidity or mortality, were not as strongly statistically significant as would be desired to support approval based upon a single clinical trial.*
-
- *In addition, the primary clinical trial did not demonstrate a significant reduction in another clinically important secondary endpoint, a composite assessment of infant mortality and morbidity.*

Question 3 (question 2 is below)

a. D**o** the data reviewed by the Committee provide substantial evidence that 17-HPC 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 17-HPC prevents preterm birth prior to 32 weeks gestational age?

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

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

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

2. Generalizability of Efficacy Results

The results of Study 17P-CT-002 demonstrated a reduction in the rate of preterm birth < 37 weeks from the **55%** incidence seen in the placebo group to the 36% incidence observed in the 17-HPC group. However, a previous large clinical trial sponsored by the NICHD (on which the sample size calculations for the current clinical trial were based) found the incidence of preterm birth prior to 37 weeks in an untreated, but similarly high risk population to be **37%**. The incidence of preterm births in the placebo arm of Study 17P-IF-001 (also conducted by the MFMU Network) was **36%**.

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

3. Potential Safety Signal 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%, 17-HPC 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 17-HPC 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 17-HPC without the need for additional pre-approval safety data?

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

4. Post-Approval Clinical Study(ies)

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)?

- The Advisory Committee made multiple recommendations for further studies which can be summarized in the following bullets:
  - Further efficacy studies
  - Studies to evaluate the potential connection between 17-HPC and miscarriages/stillbirths
  - Long term follow-up studies (possibly a registry) of children exposed to 17-HPC, including evaluation of reproductive health/genital development, fertility, and carcinogenic potential.
  - Evaluation of potential maternal complications such as depression, and gestational diabetes.
  - Elucidation of the pharmacokinetic and pharmacodynamic properties of 17-HPC.

Medical Officer's Comments:

- *The advisory committee was **supportive of approving this drug contingent on further study** primarily because there are no other available therapies for this major public health problem.*
- *There was **strong opinion that required post-marketing studies should be conducted**, particularly to further assess safety.*
- *These recommendations would support approval under the Subpart H regulation because initial approval would be based on a surrogate for infant morbidity and mortality (i.e., birth before specified gestational ages).*

2.5.3 NDA Action (October 20, 2006)

The FDA sent an Action (Approvable) Letter to the Applicant on October 20, 2006 that defined additional information required to obtain approval to market 17-HPC (referred to as HPC in the letter). The following **phase 4 clinical requirements** were outlined in the letter (Chemistry [CMC] and pharmacology/toxicology deficiencies are discussed in Section 3):

Clinical

"1. Further study is needed to provide confirmatory evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly, or through a well-established surrogate, such as the rate of preterm birth prior to 35 and 32 weeks of gestation.

2. There are insufficient data to evaluate a potential association of hydroxyprogesterone caproate (HPC) with increased risk of early fetal loss (second trimester miscarriage and stillbirth)".

Information needed to address the clinical deficiencies

"1. Submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of HPC for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510. If a placebo-controlled trial is determined not to be feasible, provide alternative study design proposals.

2. Provide a draft protocol to evaluate the potential association of HPC with increased risk of second trimester miscarriage and stillbirth. This could be assessed as a part of the confirmatory efficacy study referred to in Item No. 1 above".

Additional clinical issues that would need to be addressed postmarketing, if the product were to be approved:

1. "Completion of the additional efficacy and safety study(ies) requested above under the description of clinical deficiencies will be required as a condition of an approval under Subpart H 21 CFR 314.510 (Item No. 1 above under clinical deficiencies) or as a formal phase 4 commitment (Item No. 2 above under clinical deficiencies).

2. Long-term post treatment safety data (at least through puberty) from children whose mothers had been treated with HPC is lacking in the NDA. This information is requested and could be obtained through the establishment of a surveillance program (e.g., registry) to evaluate the effects of prenatal exposure in adolescents and young adults. Submit your proposal as to how these data would be obtained.

3. Additional developmental assessment is needed of children at ages 18-24 months whose mothers had been treated with HPC. This assessment could be obtained from the offspring of women enrolled in the confirmatory efficacy study or the safety study addressing early fetal loss. Children who screen positive for developmental delay should have a formal psychometric assessment and an additional assessment by a neurologist".

2.5.4 Complete Response (April 24, 2008)

On April 24, 2008 the new Applicant for this product, Cytyc, submitted a complete response to the Approvable letter. This response addressed the clinical, pharmacology, toxicology, and CMC deficiencies, and provided commitments regarding the post-approval issues delineated in the Approvable Letter.

In October 2007, Cytec was acquired by Hologic Inc., with Cytyc remaining a wholly-owned subsidiary. In January 2008, Cytyc entered into an agreement with KV Pharmaceutical Company (KV) whereby following approval of NDA 21-945, the NDA will be transferred to KV and marketed through their wholly-owned subsidiary, Ther-Rx Corporation.

2.6 Other Relevant Background Information

Significance of Preterm Birth

Preterm birth (defined as birth prior to 37 weeks of gestational age) is the leading cause of neonatal mortality (infant death within the first 28 days of life) and is a major cause of early childhood mortality and morbidity in the United States (Mathews 2003 [19]). As many as half of all pediatric neurodevelopmental problems can be attributed to preterm birth (Goldenberg 2002 [20]) The U.S preterm birth rate increased by 29% over the previous two decades to a high of 12.1% in 2002 (Martin 2003 [21]) Most of this increase occurred in preterm births at 32-36 weeks gestational age and is thought to be due to the increasing frequency of pregnancy in women older

than 35 years and the use of infertility treatments (Wright 2001 [22]) The rate for very early preterm births (< 32 completed weeks gestation) has remained stable at about 2% of all births; however, most perinatal/neonatal and infant mortality, and the most significant morbidity occurs in these infants (Martin 2003 [21]) Preterm births most often result from spontaneous preterm labor and preterm premature rupture of membranes [pPROM] (Lockwood 1999 [23], Iams 2003 [24], Berkowitz 1993 [25]). However, 20-30% of preterm births are considered "indicated" to avoid or minimize maternal/fetal complications (Meis 1998 [26])

Accurate prediction and prevention of PTB remains elusive (Spong 2002 [27], Iams 2001 [28], Lockwood 2002 [29], Mercer 1999 [30], Iams 1996 [31]) Most biomarkers to assess the risk of PTB have a poor positive predictive value to guide clinical decisions (Hibbard 2000 [32]). Examples of risk factors include history of previous preterm birth; multifetal gestation; and cervical, uterine, and placental structural or physiologic abnormalities.

Methods for prevention of preterm birth, including drugs, bed rest, or other interventions, have been shown in general to lack effectiveness. Tocolytic drugs may be given to reduce the frequency of uterine contractions. However, they have not been efficacious in preventing preterm birth nor have they resulted in improved newborn outcomes. Preterm birth has been described as a "common, complex disorder, stemming from heterogeneous composites of multiple gene-environment interactions." (Doland 2004 [33]) Evidence supporting this includes findings of familial aggregation, non-Mendelian heritability, high rates of recurrence, and the existence of ethnic/racial disparities.

Pathophysiology of Preterm Birth

The "syndrome" of PTB is now understood as the clinical endpoint for a number of potential causes. Four major pathophysiologic pathways have been hypothesized:

(1) inflammation/infection with its associated maternal and fetal cytokine response
(2) maternal/fetal stress with generation of placental and fetal membrane-derived corticotropin-releasing hormone, which enhances placental estrogen and fetal adrenal cortisol production
(3) abruption or decidual hemorrhage with thrombin-induced protease expression and disturbances in uterine tone
(4) mechanical stretch due to multifetal pregnancy or polyhydramnios-induced abnormal uterine and cervical distension

Infection/inflammation is the only pathologic process for which a firm causal link with prematurity has been established and for which a defined molecular pathophysiology is known (Romero 1997 [34]). It has been estimated that 40% of all preterm births occur in mothers with intrauterine infection, which is usually subclinical. The lower the gestational age at delivery, the greater the frequency of intrauterine infection (Watts 1992 [35]). The most common pathway is via ascending organisms from the lower genital tract, more commonly from an alteration in the normal vaginal flora (Romero 1988 [36]). The organisms enter the amniotic cavity and then, in some cases, will gain access to the fetus which may result in fetal sepsis or the Fetal Inflammatory Response Syndrome (FIRS) (Romero 2002 [37]), leading to possible death. The

clinician managing preterm labor must balance the risk of subclinical infection, against the sequelae of prematurity, both having the potential to cause death.

Effects of Progesterone

Progesterone exerts biologic effects not only in the myometrium and chorioamniotic membranes but also in the uterine cervix. (Word 2007 [38], Norman 1991 [39], Elliott 1998 [40], Stenlund 1999 [41], Giacalone 2001 [42]). Cervical responsiveness to anti-progestins increases with advancing gestational age, and their effects on the cervix are not always accompanied by changes in myometrial activity. A large body of evidence supports a role for progesterone in cervical ripening. Administration of anti-progestins (prostaglandins) or progesterone-receptor antagonists (mifepristone [RU486]) induces cervical ripening. Anti-progestins can induce cervical ripening without inducing labor. This suggests that a major site of progesterone action may be the cervix and perhaps not the myometrium (Romero 2007 [43]).

An unresolved issue is why progesterone administration to pregnant women, who already have a very high concentration of circulating progesterone ($> 10^{-7}$ M) would result in a therapeutic effect. It is possible that the change in progesterone concentrations at the time of spontaneous parturition in the human occurs locally and not in the systemic circulation (Romero 1988 [44], Cicinelli 1999 [45]).

Risks Associated with Late Preterm Birth

Although preterm birth is defined as a birth prior to 37 weeks gestation, the clinical significance of preterm birth is more pronounced prior to 32 weeks gestation (Martin 2003 [21]). In the U.S., infants born after 32 weeks have very low mortality rates, and relatively low long-term morbidity. However, since a larger number of preterm births occur after 32 weeks gestation, the public health importance of preventing even these later gestational age preterm births may be noteworthy. Preterm births at higher gestational ages are less well studied; therefore, the perception of outcomes at these ages may be less accurate. However, two recent studies have shed some light on the public health significance of late preterm birth.

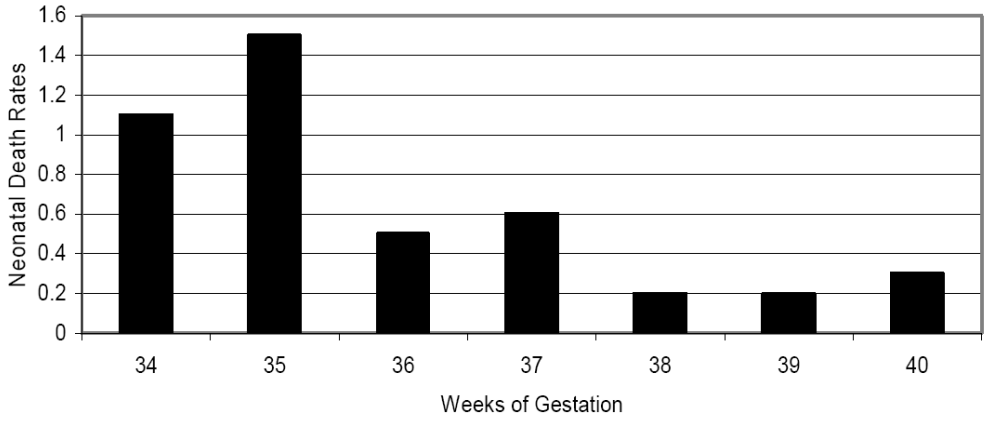
Kramer (2000 [46]) conducted a population-based cohort study using linked singleton live birth-infant death cohort files for US birth cohorts for 1985 and 1995 and Canadian birth cohorts (excluding Ontario) for 1985-1987 and 1992-1994. As compared to singletons born at term (≥37 weeks), the relative risk (RR) for infant death from all causes among singletons born at 32 through 33 gestational weeks was **6.6** (95% CI, 6.1-7.0) in the United States in 1995 and **15.2** (95% CI, 13.2-17.5) in Canada in 1992-1994; among singletons born at 34 through 36 gestational weeks, the RRs were **2.9** (95% CI, 2.8-3.0) for US infants and **4.5** (95% CI, 4.0-5.0) in Canada. Substantially increased RRs were observed overall for the neonatal periods and for death due to asphyxia, infection, sudden infant death syndrome, and external causes. The authors concluded that mildly and moderately preterm birth infants have an increased risk of death during infancy and are responsible for an important fraction of infant deaths.

McIntire and Leveno (2008 [47]) preformed a retrospective cohort study of births at the University of Texas Southwestern Medical Center between 1988 and 2005. The study included all liveborn singleton infants between 34 and 40 weeks of gestation without anomalies who were delivered to women who received prenatal care in that facility. A total of 261,194 women had singleton

births at 24 or more weeks of gestation, weighing ≥500 g. Late preterm singleton live births constituted ~9% of all deliveries and accounted for 76% of all preterm births.

Figure 1 shows the neonatal death rates from 34 to 40 weeks of gestation in singleton infants without malformations. Compared with the mortality rate at 39 weeks, there was a highly significant ($p<0.001$) increase in mortality at 34, 35, and 36 weeks of gestation; and a significant ($p=0.02$) increase at 37 weeks.

Figure 1 Neonatal Death Rates from 34 to 40 Weeks Gestation (McIntire 2008)



Medical Officer's Comment:
These studies indicate that there is more significant morbidity and mortality in late preterm births than was previously recognized.

Early (prior to 1990) Studies of 17-HPC for Preventing PTB

Near the end of the 20th century, several small studies of 17-HPC to prevent miscarriage or preterm birth were published with mixed results. Table 6 below summarizes the drug dose, entry criteria, design, number of subjects, treatment period and outcomes of these studies.

Table 6 Published Studies of the Efficacy and Safety of 17-HPC in Preventing Preterm Birth

Investigator	Drug:Dose	Entry Criteria	Design	Number of Subjects	Start Tx	Stop Tx	Outcome % PTB[A]	No. of SAB[B]
LeVine 1964[1]	17P[C]: 500 mg weekly vs. Placebo	3 SABs	RCT, DB[D] Placebo 1:1	17P: 15 Placebo: 15	< 16 wks	36 wks	17P: 7/15 (46%) Placebo: 10/15 (66%)	17P: 3/15 Placebo: 7/15
Papiernik-Berkhauer 1970[2]	17P: 250 mg q 3 days vs. Placebo	High preterm risk score	RCT Placebo 1:1	17P: 50 Placebo: 49	28 – 30 wks	8 doses	17P: 4.1% Placebo:(18.8%	No data
Johnson et al 1975[3]	17P: 250 mg weekly vs. Placebo	2 SABs or 1PTB + 1 SAB or 2 PTBs	RCT, DB Placebo 1:1	17P: 18 (4 with cerclage) Placebo: 22 (3 with cerclage)	Booking < 24 wks	37 wks	17P: 0/18 (0%) Placebo: 9/22 (41%)	17P: 3/23 Placebo: 0/27
Hauth 1983[6]	17P: 1000 mg weekly vs. Placebo	Active duty military	RCT, DB	17P: 80 Placebo: 88	16 – 20 wks	36 wks	17P: (6.3%) Placebo: (5.7%)	No Data
Yemini 1985[4]	17P: 250 mg weekly + cerclage vs. Placebo + cerclage	Hx of 2 SABs or 2 PTBs	RCT, DB Placebo 1:1	17P: 39 (all with cerclage) Placebo: 40 (all with cerclage)	Booking (12.2 wks av.)	37 wks	17P: 5/31 (16.1%) Placebo: 14/37 (37.8%)	17P: 8/39 Placebo: 3/40
Suvonnakote 1986[5]	17P: 250 mg weekly vs. no treatment	Hx of 1 PTB or 2 late SABs	Non-randomized	17P: 36 No Rx: 39	16 – 20 wks	37 wks	17P: 5/35 (14%) No Rx: 19/39 (49%)	No Data

[A] PTB=Preterm Births

[B] SABs=Spontaneous Abortions; Data for this outcome obtained both from the original articles and a meta-analysis by Keirse (see citation No. 2 below).

[C] 17P = 17-HPC

[D] RCT, Randomized Controlled Trial, DB=Double Blind

1 LeVine L. Habitual abortion. A controlled clinical study of progestational therapy. West J Surg Obstet Gynecol. 1964;72:30-6.

2 Papiernik-Berkhauer E. Double blind study of an agent to prevent pre-term delivery among women at increased risk. Ref from Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Brit J Obstet Gynaecol. 1990;97(2):149-5

3 Johnson JW, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17 α-hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med. 1975;293(14): 675-80.

4 Yemini M, Borenstein R, Dreazen E, Apelman Z, Mogilner BM, .Kessler I, et al. Prevention of premature labor by 17 α-hydroxyprogesterone caproate. Am J Obstet Gynecol. 1985;151(5):574-7.

5 Suvonnakote T. Prevention of pre-term labour with progesterone. J Med Assoc Thai.1986; 69(10):538-42.

6 Hauth JC, Oilstrap LC 3rd, Brekken AL, Hauth JM. The effect of 17 α-hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. Am J Obstet Gynecol. 1983;146(2):187-90. Source: Prepared by Medical Reviewer.

Medical Officer's Comment:

- *These studies varied in enrollment criteria, study design, length/dose of treatment and endpoints. However, all studies that enrolled subjects with a history of at least one previous PTB showed a numeric reduction in PTB in the 17-HPC arm. In addition, the LeVine study (enrolled subjects with three previous SABs) and the Papiernik study (enrolled subjects with a "high risk" score) showed a reduction in PTB in the 17-HPC arm. The only study that showed no treatment effect was the Hauth study, which enrolled women who were active duty military. There is no evidence that military duty alone puts women at increased risk for PTB.*

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The chemistry reviewer made the following conclusions:

"This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for APPROVAL."

The formulation in the phase 3 clinical trial is the same as the proposed commercial formulation. Sponsor provided comparability data between the commercial manufacturer and the 2 manufacturers of the clinical lots and they were found acceptable.

Three CMC-related deficiencies were conveyed in the Oct. 29, 2006 Approvable Letter:

1. *Since you cannot account for the degradation of the active ingredient under light-stress conditions by your HPLC method, you should develop a supporting method that can adequately detect and quantitate the potential photodegradation products. The drug product specifications should include limits for any potential impurities observed using the new method, and a detailed description of the new analytical procedure with appropriate validation should be provided.*
2. *Alternative primary and/or secondary packaging should be used to protect the drug product from light. A description and justification for the new packaging system should be submitted with appropriate letters of authorization. In addition, you should revise the drug product labeling to state that the vials should be protected from light.*
3. *Based on the limited stability data provided in the application and the out-of-specification (OOS) results for particulate matter observed at accelerated conditions, an expiration date of NMT* (b) (4) *would be appropriate for the drug product when stored at controlled room temperature, protected from light. You are encouraged to determine the cause of the OOS results for particulates under accelerated conditions, and if necessary, you should consider a different container closure for storage of your drug product.*

The chemistry reviewer provided the following summary of how these deficiencies were addressed:
"CMC points 1 and 2 were discussed with the company in December 2006 and additional data were submitted for evaluation. It was determined at that time that the additional data were satisfactory and the following agreements were made in a teleconference held on 11- Jan-2007:

1. Analysis of the additional stress light studies indicated that there was no increase in photodegradants and that it was not necessary to develop additional tests.
2. Sponsor will address the photosensitivity of the product with package labeling For CMC deficiency 3, the sponsor has provided adequate information about the identity of the particulate matter observed in the stability samples held under accelerated conditions. In the Complete Response, they submitted additional long term stability data up to 24 months on the primary stability batches and 12 months of data on process validation batches.

Late in the review cycle, the sponsor reported that due to a calculation error, the particulate matter results were reported 10-fold less than the actual values. Due to the amount of data submitted, the Amendment was coded as a major Amendment, and the review clock was extended. The recalculated and additional data (up to 30 months on the primary stability batches and 24 months on the process validation batches) were submitted and evaluated. While the particulate matter values were higher, they were well within specifications for this dosage form, and the final evaluation has not changed".

"In addition to addressing the CMC issues in the Complete Response, a minor change was made to the solution transfer process to ensure that the product is manufactured in compliance with the Medicine and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom. This change was evaluated by the microbiology reviewer to determine that it did not adversely affect FDA requirements and was found to be adequate.

An issue was raised concerning microbiological stability of the product once the product was penetrated. The issue was consulted to Microbiology, which determined that the data are adequate to support a in-use shelf-life of 5 weeks once the stopper is penetrated by the syringe. This will be reflected in the Dosage and Administration section of the label.

Based on the submitted data, *an expiration dating period of 24 months is granted when stored at controlled room temperature. In addition, the contents must be protected from light and stored in the upright position.* Sponsor has adequately addressed all CMC issues."

3.2 Animal Pharmacology/Toxicology

The pharmacology/toxicology reviewer made the following recommendation on approvability: "I recommend approval of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth."

This NDA was not approved previously due to, in part, lack of a complete reproductive toxicology study. The pharmacology/toxicology team identified the following unresolved issues:

- "Based on the information available in the published literature (Hendrickx 1987 [48]) it appears that high doses of 17-HPC are associated with increased embryo lethality in several species. The nonclinical data provided is insufficient to calculate a no adverse effect level (NOAEL) in animals.
- There is insufficient nonclinical information on potential adverse effects on postnatal development including learning, behavior, and reproduction" (Pushpalatha 2005 [49]).

The Oct. 29th, 2006 Approvable letter stated: "There is a lack of nonclinical data from a multi-generational reproductive toxicology study for this product. The following information was requested to address the toxicology deficiency:

> "A GLP-compliant, multigenerational reproductive toxicology study needs to be performed, evaluating all stages of pregnancy during which dosing will be administered in humans. The study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including learning, behavior and reproductive function, in offspring exposed *in utero*. At the time of a Complete Response submission to this approvable letter, provide, at a minimum, an unaudited interim final report of the requested study".

Cytyc conducted a multigenerational reproductive toxicology study in rats which had the following findings:

No adverse effects were observed in females or their offspring during Phase 1 of the study (time-mated F_0 females dosed three times during gestation on gestational days 8, 14, and 20) or during Phase 2 (time-mated F_0 females dosed once on gestational day 17). The F_1 pups showed comparable survival rates between treatment groups and the controls for each phase. Physical, developmental, and behavioral evaluations of the F_1 offspring for both phases did not reveal any test article-related effects during lactation or the maturation phase for these animals. Sperm evaluation of the F_1 in utero treated males revealed no negative results on any of the parameters

tested for the treatment groups as compared with the control for both phases. The mating and fertility indices for the 2 phases did not reveal any treatment-related effects. The study was concluded with the birth of the F2 generation, showing no test article-related effects on growth and survival up to lactation day 4.

The Cytyc study, in comparison the study conducted by Pushpalatha et al [49] , showed no adverse effects on reproductive health of male rats when 17-HPC was administered (i) at a more appropriate time, (ii) via a more appropriate route of administration (intramuscular vs. intraperitoneal), (iii) at even higher doses and (iv) in larger cohorts of animals. Additionally, the Cytyc study examined for the first time the issue of possible impact on female reproductive health and found no adverse effects.

In conclusion, this comprehensive and well-controlled multigenerational reproductive toxicity study of both male and female rats showed none of the adverse effects reported by Pushpalatha that raised the initial safety concern regarding reproduction. No multigenerational safety concern was identified for in utero-exposure to 17-HPC up to 30 times the proposed human dose when treatment was started very early in the gestation of the rat (before the gonads have fully developed).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

4.1.1 Evidence of the Feasibility of Conducting a Confirmatory Study

To address item 1 of the clinical deficiencies, Cytyc contracted with (b) (4) , a contract research organization, to survey obstetricians, gynecologists, and maternal-fetal medicine specialists regarding the feasibility of conducting an additional multicenter, placebo-controlled trial of 17-HPC for the prevention of recurrent preterm birth in the post-approval setting. The study design described in the feasibility survey was materially similar to the already completed NICHD study (17P-CT-002), however, with a primary outcome of preterm birth at < 35 weeks.

Potential survey participants were recruited from academic, community and private practices. Participants were directed to an online survey and asked to provide the following information: medical specialty, practice setting, practice type, subject of board certification, number of pregnancies managed (and among those the number with a previous preterm birth) whether they prescribe progesterone for prevention of recurrent preterm birth, their willingness (and their expectation of their patients' willingness) to consent to participate in a 2:1 placebo-controlled study of 17-HPC following FDA approval. Inclusion/exclusion criteria for the study were provided. Respondents were also asked to comment on any potential IRB concerns with the study design.

Of the 325 U.S. based physicians contacted to participate in the feasibility survey, 67 completed the online survey questionnaire. The highlights of the results were as follows:

- The medical specialties reported were Obstetrics/Gynecology (57%) and Maternal-Fetal Medicine (43%).
- 49% indicated willingness to participate in a post-approval, multicenter, randomized, placebo-controlled, clinical trial involving 17-HPC in women who have had at least one prior preterm birth. Those physicians willing to participate estimated that, on average, 59% of their eligible patients would consent to participate in the proposed placebo-controlled study.
- 33% indicated unwillingness to participate in such a study if 17-HPC was FDA approved for the prevention of recurrent preterm birth.
- 18% were undecided.

Medical Officer's Comments:

- *Only 325 obstetricians were contacted; it is unclear how they were selected; members of ACOG, Society for Maternal Fetal Medicine (SMFM), or large academic institutions were not specifically targeted to be surveyed.*
- *Only 67/325 (21%) completed the survey.*
- *49% of 67 respondents (32 physicians) indicated willingness to participate.*
- *The survey did not determine if institutions/department chairs were willing to support such a study. The Applicant surveyed more private practice clinicians compared to academic centers or HMOs such as Kaiser. The one exception was a military site; however, women recruited for military service are generally healthier than the general population and it would likely take a longer time to recruit from this population.*
- *The best chance to accomplish this study is to conduct the studies in countries (in addition to the U.S.) that do not routinely use the compounded form of the drug.*

During a June 2008 teleconference, the Division requested that the Applicant provide a *"higher level of assurance"* that there was interest in participating in this post-approval study, particularly amongst leading obstetrical investigators and thought-leaders (and including U.S. military and Canadian sites).

On Sept. 3, 2008, the Applicant sent the Division a follow-up from the June 2008 teleconference regarding the Feasibility Survey Data. The Applicant obtained confirmation of a preliminary level of interest in writing from leading investigators in the field of high risk pregnancy management. Of the 33 physicians from the Feasibility Survey who indicated a willingness to participate in the trial, Cytyc believes the 11 investigators listed in

Table 7 below are recognized in the field of Obstetrics as prominent investigators.

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Table 7 Prominent Investigators In Previous Feasibility Survey

Name	Title	Institutional Affiliation
Michael A. Belfort, MD, PhD	Director of Perinatal Research Professor, Maternal-Fetal Medicine	St. Mark's Hospital University of Utah Salt Lake City, UT
Vincenzo Berghella, MD	Director, Maternal-Fetal Medicine Professor, Obstetrics and Gynecology	Jefferson Medical College Philadelphia, PA
Ira M. Bernstein, MD	Director of Maternal-Fetal Medicine Director, Maternal Fetal Medicine Fellowship Vice Chair of Obstetrics Professor, Obstetrics and Gynecology	Fletcher-Allen Healthcare University of Vermont College of Medicine Burlington, VT
Andrew C. Combs, MD, PhD	Maternal-Fetal Medicine specialist in the Obstetrix Group Previous Director of the Medical Complications of Pregnancy Clinic at The Univ. of Cincinnati Medical Center	Obstetrix Medical Group Good Samaritan Hospital Campbell, CA
Dean V. Coonrod, MD, MPH	Chairman, Department of Obstetrics and Gynecology Director, Departmental and Resident Research Projects	Maricopa Integrated Health System Phoenix, AZ
Thomas M. Goodwin, MD	Professor 0f Obstetrics and Gynecology and Pediatrics Chief, Division of Maternal-Fetal Medicine Keck School of Medicine Director of the Fellowship Program in Maternal-Fetal Medicine Examiner for the American Board of Obstetrics and Gynecology	Women's and Children's Hospital University of Southern California Los Angeles, CA
George A. Macones, MD, MSCE	Mitchell and Elaine Yanow Professor and Chair, Department of Obstetrics and Gynecology	Barnes Jewish Hospital St Louis, MO
Hugh Miller, MD	Maternal-Fetal Medicine specialist in the Obstetrix Group	Obstetrix Medical Group Tucson Medical Center Tucson, AZ
Amy P. Murtha, MD	Associate Professor of Obstetrics and Gynecology Director, Maternal-Fetal Medicine Fellowship Program	Duke University Health System Durham, NC
Colonel Peter E. Nielsen, MD	Chief, Department of Obstetrics and Gynecology OB/GYN Consultant to The Surgeon General	Madigan Army Medical Center Tacoma, WA
Baha Sibai, MD	Chairman of the Department of Obstetrics and Gynecology Professor, Obstetrics and Gynecology	University of Cincinnati Medical Center Cincinnati, OH

Recent Communication with Prominent Maternal-Fetal Medicine Investigators

Over the past two months, the Applicant has sought to provide the Division with additional confirmation that the proposed post-approval safety and efficacy study is feasible and will be supported by thought leaders of the Maternal-Fetal Medicine community. The Applicant's goal was also to identify investigators who had access to significant populations of at-risk women and/or had the ability to identify other investigators to participate in the study. The individual letters confirming interest in participating in the study by these investigators are attached in *Appendix 10.1*.

United States Thought Leaders

Dr. Roberto Romero

Dr. Romero is Professor of Obstetrics and Gynecology at Wayne State University and Chief of the Perinatology Research Branch of the National lnstitute of Child Health and Human Development, National Institutes of Health in Bethesda, Maryland. The Applicant has spoken with Dr. Romero numerous times over the last two months and he has expressed his support for the proposed post-approval study and his willingness to assist us in identifying potential investigators for the study. However, due to another study that Dr. Romero will be conducting during the same time period, *he is unable to participate directly in the Applicant's proposed study*.

Dr. Vincenzo Berghella

Dr. Berghella is the Director of Maternal Fetal Medicine and Professor of Obstetrics/Gynecology at Thomas Jefferson University in Philadelphia, PA and is also a member of the Board of Directors for the Society of Maternal Fetal Medicine. Dr. Berghella has expressed his interest in participating in the proposed trial and also has suggested two other potential investigators, Drs. Leo Pereira and Jorge Tolosa. Cytyc is considering the possibility of recruiting Dr. Berghella as the lead Principal Investigator of their proposed study.

Dr. Jorge Tolosa

Dr. Tolosa is an Associate Professor of Obstetrics/Gynecology in the Division of Maternal Fetal Medicine at Oregon Health & Science University (OHSU) in Portland, OR. Dr. Tolosa founded the Global Network of Perinatal and Reproductive Health (www.gnprh.org) network through which he conducts research in pregnancy-related areas. Dr. Tolosa was recommended by Dr. Berghella and also has expressed his interest in participating in the proposed trial.

Dr. Baha Sibai

Dr. Sibai is the Professor and Chairman of the Department of Obstetrics and Gynecology at the University of Cincinnati College of Medicine. Dr. Sibai was a member of the subcommittee that was involved in the design and conduct of the original 17-HPC study sponsored by the NICHD. Dr. Sibai has expressed interest in participating in the proposed study, and has also recommended two additional investigators for participation.

Unites States Military Thought Leaders

Colonel Peter Nielsen, MD

Colonel Nielsen is the Chief of the Department of Obstetrics/Gynecology at the Madigan Army Medical Center in Tacoma, WA. He is an Ob/Gyn consultant to the Surgeon General and is the lead PI for the Department of Defense Maternal Fetal Medicine (DoD MFM) Network. Colonel Nielsen and Colonel Peter Napolitano MD, the Chairman of the DoD MFM Network, have both expressed interest in the study and have also solicited interest from almost all of the investigators in the DoD MFM Network, which manages a total of approximately 20,000 deliveries per year.

Canadian Thought Leaders

Dr. Anthony Annson (Eastern Canada)

Dr. Annson is Professor and Head of the Department of Obstetrics & Gynaecology, Dalhousie University & IWK Health Centre, Halifax. Dr. Annson had previously recruited several Canadian and international investigators for a progesterone clinical trial which was subsequently canceled prior to initiation due to lack of funding from the Canadian government. He has indicated that he is interested in participating in the proposed study and believes he could also recruit investigators from the previously cancelled study to participate.

Dr. Duncan Farquharson (Western Canada) Dr. Farquharson is Assistant Professor in the Department of Obstetrics and Gynecology at the University of British Columbia and practiced actively at the BC Women's Hospital until October 1999 when he was appointed as Director of Maternal-Fetal Medicine Services for the Fraser Health Authority and Head of Obstetrics at the Royal Columbian Hospital (one of only three tertiary obstetrics facilities in British Columbia). Dr. Farquharson has expressed interest in participating in the proposed study.

There are multiple studies underway around the world to investigate the efficacy of various progesterones in preventing preterm birth; however, only one study sponsored by Assistance Publique – Hopitaux de Paris (Patrick Rozenberg, M.D.) is evaluating the efficacy of 17-HPC in singleton pregnancies to prevent preterm birth. The entry criteria (risk factor/s for preterm birth) for this study are not known to this reviewer.

Medical Officer's Comment:

No other studies have been conducted in the United States, since the 2003 Meis publication, to investigate the effectiveness of 17-HPC to reduce PTB in women with a previous PTB. One study investigating 17-HPC in singleton gestations is underway in Paris, France and as mentioned previously, the entry criteria are not known to this reviewer. However, the investigators listed above have provided reasonable assurance that they will be willing and able to conduct the phase 4 study for the Applicant in both the U.S. and countries outside of the U.S. where 17-HPC is not currently in widespread use. Several investigators have access to particularly large populations:

- ***Dr. Tolosa*** *is the Founder and coordinator for the Global Network for Perinatal and Reproductive Health (GNPRH) (www.gnprh.org). This network provides access to large tertiary care centers both in the United States and also in middle and high income countries in Europe, South East Asia and Latin America.*
- ***Colonel Nielsen*** *is the Chief of the Department of Obstetrics/Gynecology at the Madigan Army Medical Center in Tacoma, WA and is the lead Principal Investigator for the Department of Defense Maternal Fetal Medicine (DoD MFM) Network and has access to over 20,000 pregnant women.*
- ***Dr. Farquharson*** *is Director of Maternal-Fetal Medicine Services for the Fraser Health Authority and Head of Obstetrics at the Royal Columbian Hospital (one of only three tertiary obstetrics facilities in British Columbia) and has access to more than 3100 pregnant women.*

Many of the investigators listed above have networked together as indicated in the letters submitted above, which adds further confirmation of the Applicant's ability to conduct a phase 4 study.

On Nov. 19, 2008 the Division sent the following communication to the Applicant summarizing discussion at a teleconference held that day: "The Division noted that the October 2008 publication of a revised ACOG Committee Opinion (#419) on use of progesterone for prevention of recurrent preterm birth had engendered concern and much internal discussion within DRUP regarding the feasibility of the proposed post-approval placebo-controlled trial of 17 α-hydroxyprogesterone caproate (17-HPC). The Division is worried that the ACOG statement may appear to bring premature closure to the evaluation of the safety and efficacy of 17-HPC. The specific concerns focus on three levels of feasibility necessary for successful completion of a trial:

- Whether investigators will still agree that the safety and efficacy of 17-HPC are sufficiently open questions as to induce them to enroll subjects in such a placebo-controlled study
- Whether institutional review boards (IRBs) will approve a placebo-controlled trial after 17-HPC has FDA approval and given the clinical standard of care at their institution ensuring from the ACOG statement
- Whether patients will consent to randomization that might result in assignment to the placebo arm

The Division's October 2006 approvable letter requested that the Sponsor "submit a draft protocol and evidence of feasibility for an additional multicenter, well-controlled trial to provide confirmatory evidence of efficacy and to address a potential safety signal of early fetal loss". The ramifications of the current ACOG opinion have led the Division to consider that the "evidence of feasibility" needs to exceed the currently provided letters of interest from several potential U.S. and Canadian investigators. It may be that nothing short of actual trial initiation, with enrollment of 10-20% of the planned sample size, will provide sufficient reassurance that a post-approval trial can reasonably be expected to succeed.

The Sponsor believes that the 2008 ACOG opinion is little different from the original opinion issued in 2003, and noted that their initial discussions with potential investigators about the feasibility of a placebo-controlled trial were favorable, even within the context of ACOG's initial permissive statement about use of progesterone as a treatment option for women with previous preterm birth. Many in the Division believe that the ACOG 2008 opinion is much stronger than the 2003 opinion in setting the standard of care for women with previous preterm birth, such that it may be difficult or impossible to conduct a placebo-controlled study post-approval. In fact, several investigators have noted difficulty in getting progesterone research projects approved by their IRBs in the wake of the new opinion. The Division recommended that the Sponsor re-contact the thought leaders and potential investigators and discuss whether their interest in and support for the trial has changed since the ACOG opinion.

While the Division acknowledges that a request that the Sponsor actually initiate enrollment in the trial prior to receiving approval poses a significant logistical and financial hurdle, the Division is not considering a request that the Sponsor submit final data prior to taking an approval action. However, the first cycle review found that, in addition to the single NICHD study submitted, the Division needed confirmatory evidence of efficacy as well as further exploration of a potential safety signal of early fetal loss. The Division cannot in good

conscience approve Gestiva now if there is reasonable doubt that such a confirmatory study would ever be conducted.

The Sponsor asked about two alternative options that might sidestep difficulties facing a placebo-controlled trial in the U.S.:

- Conduct of a completely foreign study
- Conduct of an alternative design, which had been discussed in the first review cycle, of two arms which evaluated the effect of staggered entry onto active drug. Instead of having one active and one placebo arm, such a study would initiate one arm immediately onto active drug, while the other arm would receive placebo until a specified gestational age, at which time they would also receive active drug.

The Division agreed that the Sponsor will likely need to explore additional ex-U.S. sites, but cautioned that it is necessary that at least some of the data come from the U.S., or at least from other North American sites with similar population demographics. A staggered entry study might provide useful data on the potential safety signal, but would be unlikely to provide confirmatory efficacy data, or none that would be as incisive as that obtained against a placebo comparator. The Sponsor will need to demonstrate that 17-HPC is superior to some treatment."

On 12 Dec. 2008 the Applicant sent the Division a revision of the original protocol (incorporated in the efficacy and safety sections below) and the results of their latest attempts to explore the feasibility of conducting the study.

Re-contact Respondents to Original Feasibility Survey Conducted in 2007

Cytyc and (b) (4) (the CRO who conducted the feasibility survey in 2007) re-contacted the respondents in the US who had previously indicated a willingness to participate in the study to specifically determine whether their willingness to participate has changed in light of the October 2008 ACOG Committee Opinion, and if, in their opinion, their IRB would be willing to approve such a study. Of the 33 original respondents, 16 were contacted; 12 of the 16 investigators continue to be interested and believe their IRBs would grant permission for them to participate in the post-approval, placebo-controlled study of 17-HPC in light of the October 2008 ACOG Committee Opinion. Four of the 16 investigators had changed their opinion and no longer feel as though the study can be conducted at their site.

Re-contact with Key Opinion Leaders (KOLs)

The Applicant also re-contacted the KOLs to understand their position in light of the recent ACOG Committee Opinion. Specifically, Cytyc inquired whether they would remain interested in participating in this study and if so, whether their IRB would, in their understanding of that IRB, still be willing to grant approval. Fourteen of the 16 KOLs and their colleagues that were previously contacted continued to be interested to participate in the post-approval study and believed IRB approval would be achieved.

International Investigators

Cytyc initiated exploration of international investigator interest (North America in participating in the post-approval, placebo-controlled study.

Table 8 is a summary of the international investigators who indicated a willingness to participate.

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Table 8 International Investigators in Participating

Investigator/Institution Name	**Location**
North America	
George Carson, MD	Regina, SK
Regina Qu'Appelle Health Region	Canada
Duncan Farquharson, MD	Vancouver, BC
University of British Columbia, North Fraser Health Region	Canada
Nancy Kent, MD	Vancouver, BC
British Columbia Women's Hospital	Canada
Amanda Skoll, MD	Vancouver, BC
University of British Columbia, British Columbia Women's Hospital	Canada
Jose Antonio Ayala, MD	Mexico City
Unidad Medica de Alta Especialidad en Ginecologia y Obstetricia	Mexico
Guillermo Alberto Jimenez, MD	Mexico City
Unidad Medica de Alta Especialidad en Ginecologia y Obstetricia	Mexico
Felipe Vatillo-Ortega, MD	Mexico City
Instituto Nacional de Perinatología Isidro Espinosa de los Reyes	Mexico
Western Europe	
Roland Devlieger, MD	Leuven
UZ Gasthuisberg Leuven	Belgium
Elisa Done, MD	Leuven
UZ Gasthuisberg Leuven	Belgium
Gian Carlo Di Renzo, MD	Perugia
University of Perugia	Italy
Nicola Rizzo, MD	Bologna
University of Bologna	Italy
Patrizia Vergani, MD	Monza
Università degli Studi di Milano-Bicocca	Italy
Herman Van Geijn, MD	Amsterdam
Frij Universitat Amsterdam	the Netherlands
Luis Cabero, MD	Barcelona
Universitari Vall D'Hebron	Spain
Irene Hoesli, MD	Basel
Universitatsspital	Switzerland
Andrew Shennan, MD	London
St. Thomas Hospital	UK
Total = 16	

As summarized in

Table 9, the Applicant has identified 55 investigators, at 46 individual sites, in 9 countries that expressed interest in this study. Cytyc states that they are continuing to identify investigators who are willing to participate in this study, both in the US and outside the US, therefore this list is not intended as a comprehensive or final list of investigators.

Table 9 Summary of Global Investigators/Sites

Regions	Investigators	Sites
United States	39	33
Canada	4	3
Mexico	3	2
Western Europe	9	8
Total	**55**	**46**

Medical Officer's Comment

- *The sites planned for the phase 4 studies will likely include populations (especially Caucasians and Hispanics) that were not greatly represented in the previous study.*

Impact of ACOG Committee Opinion

Cytyc recently spoke with Dr. Roberto Romero; it is Cytyc's understanding that Dr. Romero believes, based on his own clinical research experience, that "the recent ACOG Committee Opinion has made the feasibility of conducting the post-approval, placebo-controlled study of 17P *more challenging*. He believes there are investigators in the US who would still be willing to conduct this study in light of the ACOG Committee Opinion (and our survey confirms this), but he also believes that patient recruitment and IRB approval would be more difficult". In addition to Dr. Romero, several other investigators similarly expressed that patient enrollment may be more challenging in light of the ACOG Committee Opinion because "*reference to the ACOG Committee Opinion will need to be included in the patient informed consent".*

Medical Officer's Comments

- *The revised ACOG Committee Opinion (#419) ACOG has set a new de-facto "standard of care" to offer treatment to all pregnant women with a history of a previous preterm birth with some formulation of progesterone. This opinion will likely make it difficult to do a placebo controlled study in the U.S.*

4.4 Data Quality and Integrity

There were no concerns regarding the quality and integrity of the data that was submitted in the original review; however, not all reports from the Division of Special Investigations (DSI) were complete at the time the action was taken. Final reports were received during the current review cycle, and there were no violations that would impair the acceptability of the clinical data.

4.4.1 Institutional Review/Ethics/Consent Form:

Prior to starting the study, the protocol, informed consent, advertisements (to be used for subject recruitment), and any other written information regarding this study will be provided to the subject or the subject's legal guardian and will be approved by the IRB/IEC.

A written informed consent, in compliance with Part 50 of Title 21 of the Code of Federal Regulations (CFR), shall be obtained from each subject/legal guardian prior to entering the study

or performing any unusual or non-routine procedure that involves risk to the subject. Women who are not fluent in English will be enrolled by a person fluent in their language and both verbal and written informed consent obtained in that language; if such are not available, they will not be included.

4.5 Compliance with Good Clinical Practices

The investigator agrees that the study will be conducted according to the principles of the ICH E6 Guideline on GCP and the principles of the World Medical Association Declaration of Helsinki. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

Data Handling/Quality Assurance
All aspects of the study will be carefully monitored, by the Applicant or its designee, for compliance with applicable government regulations with respect to current GCP and current standard operating procedures.

The monitor will visit the investigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

Investigators and institutions involved in the study will permit trial-related monitoring, audits, Internal Review Board/Internal Ethics Committee (IRB/IEC) review, and regulatory inspection(s) by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the Applicant, representatives of the Applicant, the FDA, or other regulatory agency access to all study records.

4.6 Financial Disclosures

Investigators will be required to provide financial disclosure information to allow the Applicant to submit the complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR. In addition, the investigator must provide to the Applicant a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The Division stated in the October 2006 Approvable Letter the following:
"In planning your subsequent clinical trial(s), the following pharmacokinetic elements should be considered as part of the design to allow for better understanding of HPC [17P] pharmacokinetics and optimal dosing:

- Characterize the pharmacokinetics of HPC and its metabolites in pregnant women (including both plasma and urine concentrations) at several periods throughout the pregnancy.
- Assess the HPC exposure-response relationship and the effect of body weight on the pharmacokinetics of HPC via sparse sampling of all subjects.
- Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on HPC pharmacokinetics."

In consultation with the clinical pharmacologist (Dr. Tran), the following phase 4 postmarketing commitments were agreed upon by both the Division and Cytyc:

1. The sponsor will provide data characterizing the pharmacokinetics (PK) of 17 α-hydroxyprogesterone caproate (17-HPC) and its metabolites in plasma and urine in pregnant women at several periods throughout the pregnancy.
2. The sponsor will obtain sparse PK samplings as agreed to in the planned Phase 4 efficacy and safety study and analyze the data to assess exposure-response relationships (e.g., time to birth) and effect of body weight and other covariates, as needed, on the PK of 17-HPC.

There were 2 new literature reports on the in vitro and preclinical metabolism of 17-HPC since the original NDA review. The new data was consistent with and support previous findings that 17-HPC can be metabolized but the caproate ester bond appears to remain intact.

NIH – Obstetric Pharmacology Study

A study evaluating the pharmacology of 17-HPC in pregnant women with a previous history of preterm birth (ClinicalTrials.gov identifier: NCT00409825) is being conducted by the University of Pittsburgh and NIH (Principal Investigator: Steve Caritis, MD). Cytyc has spoken with Dr. Caritis regarding the status of the study and the projected completion date of December 2008. Cytyc proposes to provide to the Division a literature summary of the data that emerge from this study.

The Caritis/NIH study is enrolling approximately 60 subjects who are receiving weekly intramuscular injections of 250 mg of 17-HPC. The source of the 17-HPC study drug is (b) (4) , the same source of 17-HPC study drug used in the NICHD study (17P-CT-002). During the study, blood samples will be drawn at several periods throughout the second and third trimesters of pregnancy. The primary outcome measure is the change in the area under the concentration (AUC) vs. time curve in the second and third trimesters of pregnancy. Secondary outcome measures include standard pharmacokinetic (PK) parameters (Cmax, Tmax,

Cl/F, Clr, V/F, MRT, and t1/2); trough plasma concentrations of 17-HPC; metabolites of 17-HPC in maternal blood and urine; genotype of 17-HPC metabolizing enzymes; C-reactive protein (CRP), cortisol releasing hormone (CRH), and other progestational biomarkers; plasma progesterone, 17 alpha-hydroxyprogesterone, estradiol; fetal and neonatal outcomes including cord 17-HPC and metabolite concentrations; and maternal:fetal drug ratios.

Because of the comprehensive scope and size of the Caritis/NIH 17-HPC PK study and the invasive nature of conducting such a study, particularly in pregnant women, Cytyc believes it is not necessary or appropriate to duplicate this study. Provided that the results of the Caritis/NIH study are sufficient to characterize the PK of 17-HPC and its metabolites, Cytyc would anticipate conducting no further research in this area.

17-HPC exposure-response relationship and the effect of body weight on the PK of 17-HPC

Cytyc proposes to use a population pharmacokinetic/pharmacodynamic (PK/PD) approach to explore the exposure-response relationship and the effect of BMI on the PK of 17-HPC. A population PK model will be built using a nonlinear mixed-effect modeling approach. The structural PK model will contain PK parameters, such as clearance and volume, as fixed-effect parameters. The relationship of 17-HPC steady-state exposure with relevant PD response markers, such as gestational age at delivery, will be defined using an appropriate PK/PD model, such as an inhibitory maximum observed effect (E_{max}) model.

Cytyc has incorporated a population PK substudy into the efficacy and safety study (see the draft protocol provided as Exhibit 2-2 in Section 2 of this Complete Response). PK assessments will be made on a sparse sampling of approximately 450 subjects (300 active and 150 placebo) enrolled in the PK substudy, stratified according to BMI in order to analyze the dose-plasma concentration-time relationship of 17-HPC. Three blood samples will be drawn:

1. Before study drug dosing at either Visit 7 or 8 (i.e., Dose 5 or 6).
2. Before study drug dosing at either Visit 9 or 10 (i.e., Dose 7 or 8).
3. At a separate, non-dosing visit 1 to 4 days after Visit 10, 11, or 12 (i.e., 1 to 4 days after Doses 8, 9, or 10).

The 17-HPC exposure-response relationship will be explored by a population PK/PD approach using a nonlinear mixed effect model. The dependence of apparent clearances and volumes on BMI will be examined as the primary covariate.

Approximately 450 subjects will participate in the population PK substudy. Subjects in the PK population will be stratified based on BMI (≤ 28 and > 28), such that approximately 40% and 60% of subjects are in each BMI category, respectively. This sample size, while not based on any statistical considerations, will enable generation of a sparse sample that will permit adequate nonlinear modeling of the PK/PD effects of 17-HPC.

Effect on 17-HPC PK of concomitant medications (strong inducers or inhibitors of drug metabolizing enzymes)

Concomitant medication information will be collected throughout the efficacy and safety study. Effects of known strong inducers or inhibitors of metabolizing enzymes on PK of 17-HPC will

be examined by including them as covariates in the population PK model, if feasible.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Gestiva is indicated for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth.

6.1.1 Methods

The Applicant proposes to do two clinical trials, post-approval, under the Subpart H, 21 CFR 314.510:

- The principal study is a multicenter, randomized, double blind, placebo controlled clinical trial in women with a singleton pregnancy, aged 16 years or older, with a history of a previous singleton spontaneous preterm delivery. The protocol for this study is submitted to the Division for approval prior to beginning the study.
- A prospective, non-interventional follow-up study of children aged 18 to 24 months, born to mothers who received 17-HPC or placebo in the principal study. A draft protocol is submitted for review; however, final concurrence by the Division will occur post approval.

6.1.2 General Discussion of Endpoints

Primary Outcome

The primary outcome is preterm birth prior to 35^0 weeks of gestation. All deliveries occurring from randomization until 35^0 weeks of gestation, including miscarriages occurring from 16^0 through 19^6 weeks of gestation and elective abortions, will be included.

Secondary Outcomes

The *key secondary outcomes* of this study are to:

- Determine if 17-HPC reduces the rate of neonatal mortality or morbidity, if and only if, the rate of preterm birth < 35^0 weeks of gestation is statistically significant (i.e., hierarchical testing approach). Neonatal mortality or morbidity is measured by a composite index comprising:
    - Neonatal death.
    - Grade 3 or 4 intraventricular hemorrhage.
    - Respiratory distress syndrome.
    - Bronchopulmonary dysplasia.
    - Necrotizing enterocolitis.
    - Proven sepsis.

Exclude a doubling of the risk in the 17-HPC group compared to the placebo group of the composite of:

- fetal/early infant death, defined as
    - spontaneous abortion/miscarriage (delivery from 16^0 through 19^6 weeks of

gestation) or
    - death (from minutes after birth until 28 days of life) occurring in liveborns born at less than 24 weeks gestation.
- stillbirth (antepartum or intrapartum death from 20 weeks gestation through term), in the 17-HPC group compared to the placebo group.

Other secondary outcomes:
- Preterm birth < 32^0 weeks of gestation.
- Preterm birth < 37^0 weeks of gestation.
- Dose-plasma concentration-time data of 17P analyzed using a nonlinear mixed effects modeling (NONMEM) of a population approach and the NONMEM software (Icon Development Solutions, Ellicott City, MD). The dependence of apparent clearances and volumes on BMI examined as the primary covariate through its formal inclusion in the NONMEM models.
- Pharmacokinetic models to evaluate effects on concomitant medications that may effect the inhibition or induction of 17-HPC will be evaluated and modeled as data permit.

Additional maternal outcomes that will be measured include:
- Spontaneous preterm birth prior to 37^0 and prior to 35^0 weeks of gestation. Spontaneous delivery is defined as following premature rupture of membranes (pPROM) or spontaneous labor from 20^0-37^0 and 20^0-35^0 weeks of gestation or miscarriage from 16^0 through 19^6 weeks of gestation.
- Indicated preterm birth (generally medically/surgically induced for medical/surgical indications) prior to 37^0 weeks of gestation. Elective abortions will be defined as indicated preterm births.
- Gestational age at delivery.
- Miscarriage (delivery from 16^0 through 19^6 weeks of gestation).

Additional neonatal outcomes that will be measures include:
- The following individual components of the composite mortality/morbidity index:
    - IVH
    - RDS
    - BPD
    - NEC
    - Proven sepsis
- Birth weight.
- Seizures.
- Retinopathy of prematurity (ROP).
- Patent ductus arteriosus (PDA).
- Infant hospital days: Time from birth to hospital discharge.
- Number of days of neonatal respiratory therapy: Defined as the number of days on ventilator support and/or oxygen therapy.
- Transient tachypnea.
- Persistent pulmonary hypertension.

Medical Officer's Comment:

- *The Division provided advice to the Applicant on November19, and December 2, 2008. The Applicant agreed to the following which is reflected above in the protocol :*
    - *Change in the "key secondary" endpoint that would be analyzed in a hierarchical manner if the primary efficacy endpoint (% deliveries at <35 weeks) demonstrates statistical significance. The Division requests that the composite neonatal mortality and morbidity index be evaluated in a hierarchical manner. This will provide the needed link between the surrogate endpoint of gestational age at delivery and a clinical benefit as measured by the index. The Applicant should size the study so as to provide adequate power for evaluating the index.*
    - *Revising the safety endpoint analysis to describe ruling out a doubling of risk of early fetal loss in the 17-HPC arm rather than determining a non-inferiority margin in the rate of early fetal loss.*
    - *Revise the analysis plan to include an analysis that reflects the stratified randomization scheme, such as a Cochran-Mantel-Haenszel analysis*

6.1.3 Study Design

Type of Study:

A Phase 4, Multi-Center, Randomized, Double-Blind Study of 17 α-Hydroxyprogesterone Caproate (17-HPC) versus Placebo for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous Preterm Delivery.

Drug Product

Gestiva will be supplied as 5 mL of a sterile solution in a multiple dose glass vial. Each mL will contain 17α-hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), castor oil (28.6% v/v), benzyl benzoate (46% v/v), and benzyl alcohol (2% v/v) as preservative.

Vehicle – 5 mL multidose vials containing are identical in color and appearance to 17-HPC and have the same excipient ingredients as 17-HPC, but do not have the active compound.

Dosing Regimen

Gestiva is to be administered intramuscularly at a dose of 250 mg (1 mL) once each week beginning at 16 weeks 0 days (160 weeks) to 20 weeks 6 days (206 weeks) of gestation to week 37 of gestation or until birth.

Overall Study Plan

The proposed study is a multi-center, randomized, double-blind, vehicle-controlled clinical trial in women with a singleton pregnancy, aged 16 years or older, with a history of a previous singleton spontaneous preterm delivery. A total of 1707 subjects will be randomized in a 2:1 ratio (1138 active and 569 placebo) to receive either 17-HPC or placebo, respectively. Subjects will receive weekly injections of study drug from randomization (16^0 through 20^6 weeks of gestation) until 36^6 weeks of gestation or delivery, whichever occurs first. PK assessments will be made based on a sparse sampling of approximately 450 subjects (300 active and 150 placebo), stratified according to BMI to analyze the dose-plasma concentration-time relationship of 17-

HPC. Randomized subjects will be followed up to 30 ± 7 days after the last dose of study drug or discharge from the delivery hospitalization, whichever occurs later. Neonates of randomized subjects will be followed until at least 28 days of life. Neonates who remain hospitalized at 28 days will be followed until discharge from the birth hospitalization or 120 days after birth, whichever occurs first.

Subjects/Populations

Approximately 1707 subjects will be enrolled and randomized at multiple sites both in the US and at sites outside the U.S. A Subject is considered enrolled in the study if she receives the trial injection.

Inclusion Criteria

1. Age ≥ 16 years.
2. Singleton gestation.
3. Project gestational age 16^0 weeks of gestation or more and less than or equal to 20^6 weeks of gestation at the time of randomization, based on clinical information and evaluation of the first ultrasound.
4. Documented history of a previous singleton spontaneous preterm delivery. Spontaneous preterm birth is defined as delivery from 20^0 to 36^6 weeks of gestation following spontaneous preterm labor or pPROM. Where possible, the gestational age of the previous preterm birth (referred to as the qualifying delivery) should be determined. If the gestational age at delivery is obtained directly from the medical record and more than one gestational age appears, the latest will be used. As a validation of the gestational age of the previous delivery, if the infant weighed more than 3300 grams (the birth weight 90th percentile for 36 weeks gestational age), this will not qualify as preterm. The previous preterm delivery cannot be an antepartum stillbirth.

Exclusion Criteria

1. Multifetal gestation.
2. Known major fetal anomaly or fetal demise. An ultrasound examination between 14^0 through 20^3 weeks of gestation must be performed to rule out fetal anomalies.
3. Progesterone treatment in any form (e.g., vaginal, oral, intramuscular) during the current pregnancy.
4. Heparin therapy during the current pregnancy or a history of thromboembolic disease.
5. Maternal medical/obstetrical complications including:
    - Current or planned cerclage
    - Hypertension requiring medication
    - Seizure disorder
6. Subjects with a uterine anomaly (uterine didelphus or bicornuate uterus) or with uterine fibroids are eligible for the trial.
7. Unwillingness to comply with and complete the study.
8. An ultrasound at 14^0 through 20^3 weeks of gestation cannot be arranged before randomization.

9. Participation in an antenatal study in which the clinical status or intervention may influence gestational age at delivery.

10. Participation in this trial in a previous pregnancy. Women who were screened in a previous pregnancy, but not randomized, do not have to be excluded.

Medical Officer's Comments:

- *The inclusion/exclusion criteria are acceptable.*
- *Allowing adolescents ≥ 16 years old should provide adequate data in the adolescent population.*

Procedures/Daily Visits

Each subject will be seen for weekly study visits to administer intramuscular injections of study drug. The weekly visits will occur until the subject is 36^6 weeks of gestation or delivery, whichever occurs first. Three blood samples will be collected from approximately 450 subjects (300 active and 150 placebo) for the population PK analysis at specified visits during the trial. If the treatment is interrupted for any reason, the subject will be encouraged to resume treatment with the study drug and continue until 36^6 weeks of gestation or delivery, whichever occurs first.

At each study visit, the subject will be asked about possible AE(s) experienced since the last injection, the use of concomitant medications, and information related to additional risk factors for miscarriage will be collected. A full schedule of assessments is provided in Table 10 below.

The subject's ability to comply with the study protocol and procedures will be assessed at the Initial Evaluation (Visit 2). The subject will receive an injection (referred to as the trial injection) of the placebo (1 mL inert oil). The subject will be told that this injection does not contain the active drug but is a test for compliance with the treatment regimen and for any unusual reactions to the injection. She will be asked to return within one week for randomization. Subjects may return any time from three to seven days after the trial injection, as long as randomization occurs from 16^0 through 20^6 weeks of gestation.

Overall subject compliance with study treatment will be assessed by determining the number of injections received. The date of each injection will be recorded in the subject's case report form (CRF). All enrolled subjects will be followed until the End of Study Visit, 30 ± 7 days after the last dose of study drug or delivery, whichever occurs later. The primary outcome measure and secondary maternal outcome measures will be determined based on the date of delivery and the estimated date of confinement (EDC), which is evaluated in a standardized manner. Neonates of randomly assigned subjects will be followed until discharge from the birth hospitalization or 120 days after birth, whichever occurs first. The secondary neonatal outcome measures will be determined from review of the neonatal medical record and will be based on standardized definitions of the morbidity measures.

PK assessments will be made based on a sparse sampling of approximately 450 subjects (300 active and 150 placebo) stratified according to BMI (≤ 28 and > 28) to analyze the dose-plasma concentration-time relationship of 17-HPC. Three blood samples will be drawn:

1. Before study drug dosing at either Visit 7 or 8 (i.e., Dose 5 or 6).

2. Before study drug dosing at either Visit 9 or 10 (i.e., Dose 7 or 8).
3. At a separate, non-dosing visit 1 to 6 days after Visit 10, 11, or 12 (i.e., one to six days after Doses 8, 9, or 10). subjects will be stratified 2:1 (17-HPC: placebo) such than an even distribution of samples will be drawn on day 1, day 2, day 3, day 4, or day 5/6 post-dose. This will result in approximately 60 17-HPC and 30 placebo samples on each day.

The BMI-dependence of apparent clearance and volumes of distribution will be examined as the primary covariate. Pharmacokinetic models to evaluate effects on concomitant medications that may affect the inhibition or induction of 17-HPC will be evaluated and modeled as data permit.

Table 10 Schedule of Events for the Study

Procedures	**Baseline[a]**	**Initial Evaluation[b]**	**Active Treatment Period[c]**			
	Visit 1	**Visit 2**	**Visits 3 to 36^6 Weeks of Gestation or Delivery**	**Delivery and Hospitalization**	**Neonate Follow-up[d]**	**End of Study Visit[e]**
Informed consent[f]	X					
Medical records release[g]	X					
Medical/obstetrical history	X					
Demographic information/social history	X					
Ultrasound (14^0 through 20^3)	X[h]					
Document previous preterm delivery	X					
Brief physical examination[i]	X					
Height	X					
Weight	X	X	X			
Prior medications[j]	X	X				
Concomitant medications[k]			X	X		X
Determine project gestational age and estimated date of confinement	X					
Schedule initial evaluation and randomization visit	X					
Trial injection		X				
Randomization[l]			X			
Collect blood sample for pharmacokinetic analysis			X[m]			
Study drug administration			X[n]			
Record adverse events (AEs)[o]		X[p]	X	X		X
Record pregnancy complications			X	X		
Record additional risk factors of miscarriage	X			X		
Maternal delivery information				X		
Neonatal information[q]				X	X	

[a] Visit will occur within 7 days before randomization.

[b] No later than 20^3 weeks of gestation and at least 3 days before randomization.

[c] Subject will report to the clinical site weekly for study drug administration until 36^6 weeks of gestation or delivery, whichever occurs first.

[d] The status of all neonates (alive or dead), regardless of when they are delivered and discharged from the hospital, will be obtained 28 days after delivery. If the neonate has been discharged from the birth hospitalization, the subject will be contacted by telephone 28 days after delivery to obtain the neonate's status.

[e] Should occur 30 ± 7 days after the last dose of study drug or 30 ± 7 days after delivery, whichever occurs later.

[f] To be completed before performing any baseline procedures.

[g] Must be signed by subject/legal guardian in order to obtain medical records of previous deliveries.

[h] If a 14^0 to 20^3 weeks of gestation ultrasound to rule out fetal anomalies has not been performed as part of standard prenatal care, one must be performed prior to randomization.

[i] A brief physical examination including a visual head-to-toe inspection of the subject's anterior and posterior torso and extremities.

[j] "Prior medications" includes all medications taken during pregnancy from the estimated date of confinement until study drug is randomly assigned.

[k] Concomitant medications must be recorded in the case report form through the End of Study Visit.

[l] Between 16^0 and 20^6 weeks of gestation.

[m] Three blood samples will be drawn from the PK population at the following times: (1) Before study drug dosing at either Visit 7 or 8 (i.e., dose 5 or 6). (2) Before dosing at either Visit 9 or 10 (i.e., Dose 7 or 8). (3) At a separate, non-dosing visit 1 to 6 days after Visit 10, 11, or 12 (i.e., 1 to 6 days after Doses 8, 9, or 10). Patients will be stratified 2:1 (17-HPC:placebo) such that an even distribution of samples will be drawn on day 1, day 2, day 3, day 4 or day 5/6 post-dose.

[n] Study drug will be administered weekly (once every 7 ± 2 days) from randomization (Visit 3) through 36^6 weeks of gestation or delivery, whichever occurs first.

[o] All subjects, regardless of when they deliver, should be contacted for an End of Study Visit to obtain AE information including medications to treat AE(s). The contact can be either in person or by telephone and should occur 30 ± 7 days after the last dose of study drug or 30 ± 7 days after delivery, whichever occurs later.

[p] AEs are recorded from administration of the trial injection through the End of Study Visit including medications to treat the AE. Preterm birth is an anticipated outcome and is not considered an AE.

[q] Neonates will be followed until at least 28 days of life. Neonates who remain hospitalized at 28 days will be followed until discharge from the birth hospitalization or 120 days after birth, whichever occurs first.
Source: Complete Response Study Report: 21,945

Restrictions

No attempt will be made to alter or mandate clinical management of the subjects. However, the *use of other prophylactic tocolytic drugs is discouraged*. If complications of the pregnancy arise, (for example, *need for a cervical cerclage*, or detection of fetal anomaly/trisomy, or hospitalization for any reason including preterm labor) continuation of treatment will be at the discretion of the clinician managing the subject. These complications may not necessarily be indications for stopping treatment. Thus, if a subject is hospitalized, administration of the study drug should continue during hospitalization, if possible, as well as following discharge.

Medical Officer's Comment:

- *Women with a current or planned cerclage will be excluded; only unplanned cerclages will be allowed. The issue of allowing cerclage in these types of studies has been controversial. This reviewer thinks the Applicant has provided a reasonable compromise.*

Subject Withdrawal/Lost to Follow-up

Subjects will be considered withdrawn from study drug if they are prematurely discontinued from administration of study drug (i.e., prior to the anticipated full course of study drug therapy for a reason other than delivery). The subject will remain on study and at a minimum, delivery data will be obtained. A subject will be considered withdrawn from the study if the subject delivery data are not obtained or if attempts to contact the subject for end of study assessments are unsuccessful. Randomized subjects who are withdrawn from the study will not be replaced.

Statistical Considerations:

A total of 1707 pregnant women (1138 active and 569 placebo) will be enrolled in the study. In 3 studies of high-risk pregnant women, the rate of preterm birth < 35^0 weeks of gestation in women receiving placebo ranged from 26.5% to 30%. Using a 2:1 randomization of subjects to 17P and placebo, respectively, a total sample size of 1707 subjects is sufficient to detect a reduction of approximately 30% in the rate of preterm birth < 35^0 weeks of gestation (from 30% to 21%). The sample size was calculated assuming a type I error (2-sided) of 5% and a power of 98%. The effect size was chosen to represent a clinically significant reduction.

A sample size of 1707 subjects is sufficient to detect a clinically significant reduction in the secondary outcome of the neonatal composite index. A total of 1665 liveborn infants are required to detect a reduction of 35% in the rate of the composite index (from 17% to 11%) with a power of 90% (assuming a two-sided type I error of 5%). Assuming 2.5% of pregnancies will result in miscarriage or stillbirth, an additional 42 women need to be enrolled for a total of 1707 women. There is also sufficient power to detect clinically significant reductions in the secondary outcomes of delivery < 32^0 and < 37^0 weeks of gestation, as indicated in Table 11:

Table 11 Sample size Calculation

Secondary Outcome	Outcome Rate in Placebo Group	Percent Reduction	Power
Neonatal Composite Index	17%	35%	90%
Delivery < 32_0 weeks of gestation	20%	33%	92%
Delivery < 37_0 weeks of gestation	40%	33%	>99%

Source: Information Request – Statistical Analysis - Complete Response Submission

Assuming a 4% fetal/early infant death rate with a two-sided alpha of 5%, a sample size of 1707 subjects provides 82.8% power to rule-out a doubling in the risk of fetal/early infant death (i.e., the upper bound of the confidence interval for the relative risk of 17P compared to placebo will be ≤2.0). A fetal/early infant death rate of 4% is based on the results of Study 17P-CT-002 (the NICHD trial).

Approximately 450 subjects will participate in the population PK substudy. Subjects in the PK population will be stratified based on BMI (≤ 28 and > 28), such that approximately 40% and 60% of subjects are in each BMI category, respectively. Additionally, for the third blood sample draw, patients will be stratified 2:1 (17P: placebo) such that an even distribution of samples will be drawn on day 1, day 2, day 3, day 4 or day 5/6 post-dose. This sample size, while not based on any statistical considerations, will enable generation of a sparse sample that will permit adequate nonlinear modeling of the PK/PD effects of 17-HPC.

Five populations will be defined for analyses:

- Intent-to-treat (ITT) Population: ITT Population will consist of all randomized subjects. All subjects will be analyzed in the group to which they were randomized regardless of whether the subject received study drug.

- Modified ITT (MITT) Population: MITT Population will consist of all subjects in the ITT Population with outcome data of delivery date available.
- Per-Protocol (PP) Population: PP Population will consist of all subjects who are compliant with the study protocol. Each subject will be classified as compliant or not with the protocol based on the following criteria: subject was fully eligible (met all inclusion and had none of the exclusion criteria), at least 90% compliant with study drug, and outcome data available.
- Safety Population: The Safety Population will consist of all subjects who received any amount of study drug.
- PK Population: The PK Population will consist of subjects who received study drug and had PK data appropriate for analysis.

Inferential statistical analyses as specified will be conducted and all comparisons will be between the 17-HPC and placebo groups. An alpha level of 0.05 will be used for the primary and secondary analyses.

Primary Efficacy Outcome Measure

The primary efficacy outcome measure will be the proportion of subjects who deliver prior to 35^0 weeks of gestation. The primary efficacy analysis will utilize the ITT population. The percentage of subjects with a preterm birth < 35^0 weeks of gestation will be determined as the point estimate of the survival function from a staggered entry Kaplan-Meier analysis (which adjusts for gestational age at randomization) using time from randomization until delivery as the analysis variable. Subjects with missing outcome data will be censored on the date last known to be pregnant. Significant differences between the 17-HPC and placebo group in the proportion of subjects who deliver prior to 35° weeks gestation will be determined using a Cochran-Mantel-Haenszel test stratified by gestational age at randomization, where the effective sample sizes for each treatment group will be derived from Greenwood's formula.

A hierarchical testing approach will be utilized. Statistical significance will be determined for the primary outcome of preterm birth <35^0 weeks of gestation in the ITT population at the 0.05 significance level. If and only if the primary outcome is significant, the secondary outcome of preterm birth the percent of neonates with the neonatal composite index (liveborn infants only of subjects in the MITT Population) will be tested for significance at the 0.05 level.

The percentage of subjects who deliver prior to 35^0 weeks of gestation will also be determined for subjects who received at least one dose of study drug (the Safety population) and for the PP population using the same analytic method as described above for the ITT population.

If there are baseline imbalances between the treatment groups with respect to prognostic factors such as the number of previous preterm deliveries, an adjusted analysis of the primary outcome measure will be conducted using a Cox regression model. An additional analysis of the primary efficacy outcome will be performed to determine if there is a treatment-by-site interaction. Treatment-by-site interaction terms will be included in a Cox regression model to determine if there is consistency of results across the sites.

Secondary Outcomes

Analyses of the secondary maternal outcomes (delivery < 32^0 and < 37^0 weeks of gestation) will be conducted using the ITT, Safety and PP populations. The number and percentages of subjects with delivery < 32^0 and < 37^0 weeks of gestation will be presented by treatment group and will be determined using the same analytic method as described above for the primary outcome. The number and percentage of subjects (MITT Population) and whose neonates died liveborn infants of subjects in the MITT Population) will also be presented by treatment group. Differences between treatment groups will be analyzed using the Cochran-Mantel-Haenszel test stratified by gestational age at randomization.

Medical Officer's Comments:

- *As stated previously, the hierarchical testing method is acceptable to this reviewer.*
- *During the trial, an external and independent data safety monitoring board (DSMB) will meet periodically to review safety data. Since the DSMB will not be reviewing efficacy data, no adjustment to the alpha level is required.*

Additional Analyses

The numbers and percentages of subjects with a spontaneous preterm birth prior to 37^0 and 35^0 weeks of gestation, and indicated preterm birth prior to 37^0 weeks of gestation, will be determined and analyzed from a staggered Kaplan-Meier analysis as indicated above for the primary outcome. The number and percentages of subjects with a miscarriage and the numbers and percentages of neonates who had RDS, BPH, IVH, sepsis, NEC, ROP, PDA or seizures will be presented by treatment group. Differences between treatment groups will be analyzed using the Cochran-Mantel-Haenszel test stratified by gestational age at randomization.

Descriptive statistics of gestational age at delivery, birth weight, infant hospital days and days of neonatal respiratory therapy will be provided and the Wilcoxon Rank Sum test will be used to test for statistically significant differences between the 17-HPC and placebo groups.

Interim Analyses

During the trial, an external and independent DSMB will meet periodically to review safety data. The timing of the DSMB reviews and scope of the safety review will be detailed in the DSMB Charter. The DSMB Charter will indicate whether the data will be reviewed in a blinded or unblinded manner.

Medical Officer's Comments

- *The proposed study will be the confirmatory study for the efficacy findings of Study 17P-CT-002. The medical officer's and statistician had multiple discussions with the Applicant and the agreed upon statistical analysis is included in the revised protocol described above.*

6.1.4 Efficacy Findings (Literature Update)

SELECTED PUBLICATIONS SINCE FEBRUARY 2006

In recent years data has been published to suggest that the maternal site of initiation of preterm

labor involves the cervix, perhaps more than the uterus. Several clinical studies listed below support this theory in part by suggesting that 17-HPC may exert some effects on the cervix:

- One study *compared 17-HPC* [N=31] *with Cerclage* [N=33] to prevent PTB in subjects with a short cervix between 16 and 24 weeks gestation: gestational age was not different between the two treatment groups. (Rust 2006 SMFM Abstract [50]).
- Two studies were published based on other sources of progesterone (vaginal progesterone; Prochieve®); efficacy was demonstrated when the at-risk population was defined by short cervix as a risk factor but not when risk was defined by previous PTB:
    - One study was a randomized, double-blind placebo-controlled trial in women with a cervical length of ≤ 15 mm in 413 women: 260 of the 413 women were randomized to receive vaginal progesterone (200 mg each night) or placebo from 24 to 34 weeks gestation. Spontaneous delivery before 34 weeks gestation was less frequent in the progesterone group than in the placebo group (Fonseca 2007 [8]).
    - The other study randomized 659 pregnant women with a history of spontaneous preterm birth who started study treatment between 18^0 and 22^6 weeks gestation (309 Prochieve®, (90 mg daily; 302 placebo). Prochieve® was not effective in this population; however, an ad-hoc analysis demonstrated that the progesterone group had significantly less cervical shortening than the placebo group at the 28 week ultrasound exam (O'Brien 2007a [9])

Multiple gestation is currently under further exploration to determine if a higher dose is required:

- One multicenter, randomized, double blind, placebo-controlled NICHD sponsored study of 17-HPC to prevent PTB in *twin gestations* [17-HPC N=325; placebo N=330]: did not demonstrate efficacy (Rouse 2007 [10]).

Medical Officer's Comments:

- *There are no new data that provide additional support for efficacy of 17-HPC in women at risk for PTB.*
- *PTB in multiple gestation is thought to be mostly due to "over-stretching" of the uterus as opposed to an inflammatory response resulting from disruption of the cervical/vaginal ecology, which is thought to be the major factor in singleton PTB. There was a greater expectation that 17-HPC would be effective in multiple gestations because of this proposed mechanism. Further study is underway to determine if a higher dose is needed.*

Gestational age or the occurrence of contractions prior to the onset of treatment with 17-HPC has been examined:

- One randomized study evaluated the effectiveness of 17-HPC use *after the onset of labor*: [30 in each arm], using a higher dose of 17-HPC (341mg), demonstrated a statistically significant reduction of PTB in the 17-HPC arm. (Facchinetti 2007 [51]).
- Two retrospective studies (both using the almost the same Matria Healthcare database) evaluating the effect of *gestational age at 17-HPC initiation* showed conflicting results: One study [17-HPC began at 16-20.9 weeks (N=599), compared to 17-HPC beginning at 21-26.9 weeks (N=307): there was no difference in gestational age at delivery between the two groups (How 2007 [52]). The other study is based on a *patient population that either overlaps*

significantly or is totally contained in the dataset analyzed and published in September 2007 by How 2007. The sample size was 156 women who initiated 17-HPC at 16-20 weeks' gestation and 119 women who initiated 17-HPC at 21-26 weeks' gestation: there was also no difference in gestational age at delivery between the two groups; however, a numerically greater percentage of women with later initiation of 17-HPC delivered at <37 weeks. Gonzalez-Quintero 2007b [11]

Additional *in-vitro* data have been published, which will eventually elucidate mechanisms, kinetics etc.

A more detailed description of the above referenced studies is located in Appendix 10.3

6.1.6 Efficacy Conclusions

The efficacy results of study 17P-CT-002 are summarized in Table 12.

Table 12 Proportion of Subjects with Delivery at <37^0, <35^0, <32^0, and <28^0 Weeks

Data Source	17-HPC (N=310)	Vehicle (N=153)	Mean Treatment Differences [A] and 95% Confidence Interval [B]
	%	%	
<37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
<35^0 weeks	21.3	30.7	-9.4% [-18.7%, -0.2%]
<32^0 weeks	11.9	19.6	-7.7% [-16.1.%, -0.3%]
<28^0 weeks	9.4	10.5	-1.1% [-7.4%, 5.2%]
Composite Neonatal Morbidity Score [c]	11.9	17.2	0.1194 (nominal P value)

[A] Chi-square test.

[B] The confidence intervals, based on a t-test, are adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, the final p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

Source: FDA statistical analysis of Applicant's data from Study 17P-CT-002.

c The composite neonatal morbidity measure counted any liveborn infant who experienced death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC. P-values have not been adjusted for multiple comparisons.

Source: Table 11-8, Final Report for Study 17P-CT-002.

The efficacy results of prevention of PTB at < 35 weeks and < 32 weeks (all centers) were not statistically persuasive, with the upper bound of the confidence interval approaching 0: with a -9.4% [-18.7%, -0.2%] reduction in births less than 35 weeks; -7.7% [-16.1.%, -0.3%] reduction in births at less than 32 weeks.

The frequency of experiencing an event on the composite index of neonatal mortality/morbidity was lower in the 17-HPC group (11.9%, 35/295 infants) than in the vehicle group (17.2%, 26/151 infants) but the between-group difference was not statistically significant.

The ACRHD meeting held on August 29, 2006 [53] reached the following conclusions about efficacy:

- Prevention of PTB at <35 weeks gestation and especially <32 weeks are better surrogate endpoints for infant/childhood outcome than is <37 weeks.
- By a 12 to 9 majority, the ACRHD concluded that this single trial provided substantial evidence that 17-HPC prevents preterm birth prior to 35 weeks gestational age; however, by 14 to 7, the ACRHD believed that the trial did NOT provide substantial evidence for prevention of PTB at <32 weeks. Virtually all members (19 to 2) agreed that the trial did not provide substantial evidence of a benefit in neonatal mortality/morbidity.
- The ACRHD was primarily supportive of approving this drug, with the stipulation that another confirmatory clinical trial be conducted for safety and efficacy. One of the major reasons for needing a confirmatory trial related to the higher than expected PTB rate in the vehicle-treated arm.
- The majority (13 to 8) believed that this trial could be conducted post-approval. A major consideration for the ACRHD was that there are no other available therapies for this major public health problem.

Medical Officer's Comments:

- *The ACRHD was not aware of the disproportionate contribution of subjects from the University of Alabama in study 17P-CT-002.*
- *The disproportionate number of black (African American) subjects was not mentioned in the FDA presentation to this committee*.

The major weakness of the original application in demonstrating efficacy was that it relied for evidence of effectiveness on a single "multicenter" study which did not include a population that was representative of the United States population:

- The percentage of black (African American) subjects in this study was 59%; during the same time frame, the percentage of blacks (African Americans) in the U.S. was 12%. Although the odds ratio of PTB in black couples is 2.4% greater than white couples (Simhan 2008 [2]), and it is prudent to include a disproportionately higher number of blacks (African Americans) in this type of study, this study still does not represent the spectrum of PTB in the U.S..

Other limitations of the study included:

- There was imbalance in the contribution of the centers. One center (University of Alabama) out of 19 centers in the MFMU Network contributed almost 30% of all subjects. The reduction in PTB < 32 weeks at the University of Alabama center was much more pronounced than in all other centers combined (see table 3) and appears to have driven the significance of the results at <32 weeks.
- The preterm birth rate of 54.9% in the vehicle arm was considerably greater than the background rate of 36% used to power this study. The rate of 54.9% preterm births, is also considerably higher that of the control arm (36%) in another Maternal-Fetal-Medicine Network study, the Home Activity Uterine Monitoring study. The PTB rate of 37.1% in 17-HPC arm is no lower than the PTB rate of 36% in the control arm of the Home Activity Uterine Monitoring study.
- The efficacy results of prevention of PTB at < 35 weeks and < 32 weeks (all centers), while statistically significant, were not statistically persuasive, with the upper bound of the

confidence interval around the difference between 17-HPC and placebo approaching 0: -9.4% [-18.7%, -0.2%] reduction in births less than 35 weeks; -7.7% [-16.1.%, -0.3%] reduction in births at less than 32 weeks.

Medical Officer's Comments:

- *The generalizability of the results of this study to the U.S. population is questionable. The subjects were disproportionately very high risk, black (African American) subjects who were disproportionately from one clinic that serves an impoverished area of Alabama.*

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods

7.1.1 Evaluation of Miscarriage/Pre-viable Infant Deaths and Stillbirths

Study 17P-CT-002

In the NDA Approvable Letter, the FDA stated that there is "insufficient data to evaluate a potential association of hydroxyprogesterone caproate (HPC) with increased risk of early fetal loss (second trimester miscarriage and stillbirth)."

The FDA is concerned that in Study 17-CT-002, there was a trend toward an increased risk of miscarriage and stillbirths in the 17-HPC treatment arm. Despite a trend toward a decrease in neonatal death, there was no net survival benefit (see Table 13).

Table 13 Miscarriages, Stillbirths, and Neonatal Deaths

Pregnancy Outcome	17OHP-C N=306 n (%)	Placebo N=153 n (%)	Nominal P-value [A]
Miscarriages <20 weeks gestation	5 (1.6)	0	0.1746
Stillbirth	6 (2.0)	2 (1.3)	0.7245
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.1159
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.6887**

[A] No adjustment for multiple comparisons.
Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

Since there was an increase in infant deaths in births from 20-24 weeks in study 17P-CT-002, we are interested in combining miscarriages with deaths in pre-viable liveborns. Table 14 below provides the estimated rates of fetal/neonatal deaths, accounting for time on study drug, up to 24 weeks gestation.

Table 14 Estimated Cumulative Rates of Fetal and Neonatal Deaths Study (17-CT-002)

Week of Gestation	17-HPC %	Placebo %
16	0.0%	0.0%
17	0.0%	0.0%
18	0.0%	0.0%
19	2.3%	0.0%
20	3.5%	0.0%
21	6.3%	0.8%
22	6.6%	0.8%
23	7.2%	1.4%
24	7.2%	3.3%

Source: Statistical Review of NDA 21-94, Table 3.2, Estimated rates of fetal and neonatal Deaths, accounting for time on study drug.

New Protocol

In the protocol submitted in the Complete Response, fetal/neonatal deaths will be evaluated as a secondary (safety) outcome to rule out a doubling of the hazard ratio in the rate of miscarriages/deaths in liveborns less than 24 weeks or stillbirths greater than 20 weeks in subjects who receive 17-HPC versus those who receive placebo.

Analysis of the outcome of fetal/early infant death will be conducted in the ITT Population. The relative risk of fetal/early infant death for the 17-HPC group relative to the placebo group will be determined using the Cochran-Mantel-Haenszel procedure stratified by gestational age at randomization. A two-sided 95% confidence interval (CI) for the relative risk will be constructed using the method of Cochran-Mantel-Haenszel adjusted for gestational age at randomization. If the upper bound of the CI is less than or equal to 2.0, a doubling in the risk of fetal/early infant death can be ruled out. Treatment-by-gestational age at randomization interaction terms will be included in a logistic regression model to determine the relationship, if any, between gestational age at randomization and the risk of fetal/early infant death in the 17-HPC group compared to the placebo group.

Medical Officer's Comment:

- *The Applicant addressed the Division's requests in their proposed evaluation of fetal/early infant death:*
    - *Their analysis will account for the gestational age at which the subject is randomized.*
    - *Their analysis will rule out a doubling of the risk of fetal/early infant death.*

Qualitative Evaluation of Stillbirths

The etiology of a death following a live birth may be different from that of a stillbirth/fetal death/in-utero fetal loss. The following assessments will be undertaken, as recommended by the Stillbirth Collaborative Research Network of the NICHD, to investigate the cause of stillbirth/fetal death/in-utero fetal loss (Silver 2007 [54]).

- Perinatal autopsy and placental evaluation by a pathologist with expertise in perinatal pathology
- Karyotype
- Antibody screen
- Serologic test for syphilis
- Screen for fetal-maternal hemorrhage (Kleihauer-Betke or other)
- Urine toxicology screen
- Parvovirus serology

If there is clinical suspicion, the following tests will be considered:

- Lupus anticoagulant screen
- Anticardiolipin antibodies
- Factor V Leiden mutation
- Prothrombin G20210A mutation
- Screen for protein C, protein S, and Antithrombin III deficiency
- Uterine imaging study

Medical Officer's Comment:
In the advice letter sent to the Applicant on 30 July 2008, the FDA requested that "every attempt should be made to ensure that the recommended work-up is undertaken to determine the cause of death for each stillbirth/fetal death in-utero as described above. In a letter sent on 28 August 2008, the Applicant agreed to this.

7.1.2 Collecting and Reporting of Adverse Events

Any medical condition that is present at the time that the subject is screened but does not deteriorate will not be reported as an adverse event (AE). However, if it deteriorates or worsens significantly from baseline at any time during the study, it should be recorded as an AE. A treatment-emergent AE (TEAE) is defined as any event not present prior to exposure to study medication or any event already present that worsens in either intensity or frequency following exposure to study medication from trial injection at Initial Evaluation through End of Study. A serious adverse event (SAE) is defined as any event that results in maternal, fetal, neonatal death; is immediately life threatening; requires subject hospitalization for reasons other than pregnancy complications and preterm delivery; or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. For the purposes of this study, hospitalization due to pregnancy complications, including preterm labor/pPROM that does not result in delivery, are expected and will be recorded on the subject's CRF and not reported as an SAE. However, other pregnancy complications requiring hospitalization such as preeclampsia, chorioamnionitis, uncontrolled diabetes, etc. will be reported as an SAE.

AEs will be assessed from the time the subject receives the trial injection through 30 ± 7 days after the last dose of study drug or after delivery, whichever occurs later. At every study visit, subjects will be asked a standard question to elicit any medically-related changes in their well-

being. They will also be asked if they have been hospitalized, had any accidents, used any new medication, or changed concomitant medication regimens (both prescription and OTC medications). All subjects, regardless of when they deliver, will be contacted for an End of Study Visit to obtain AE information, including medications to treat AE(s). The contact can be either in person or by telephone and should occur 30 ± 7 days after the last dose of study drug or after delivery, whichever occurs later.

All AEs reported or observed during the study will be recorded in the AE CRF. Information to be collected includes type of event, date of onset, investigator-specified assessment of severity and relationship to study drug, date of resolution of the event, and seriousness. Treatments for AEs will be recorded on the concomitant medications CRF. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states will also be reported. All AEs will be followed to adequate resolution. Medical Dictionary for Regulatory Activities (MedDRA®) version 10.1 or higher will be used to code all AEs.

Changes in the severity of an AE will be recorded to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent (events occurring at irregular or infrequent intervals) will require documentation of onset and duration of each episode. Safety analyses will be conducted in the Safety Population. Summaries will be provided for all AEs. The incidence of AEs will be presented by system-organ class, higher level term and preferred term according to MedDRA, relationship to study treatment, severity and seriousness. AEs leading to premature discontinuation from the study drug will be summarized in a table.

Medical Officer's Comments:

- *The Applicant will add routine questions to assess the unlikely but possible risk of pulmonary microemboli – cough and shortness of breath.*
- *An external and independent DSMB will meet periodically to review safety data. The DSMB Charter will indicate whether the data are reviewed in a blinded or unblinded manner.*
- *The Applicant changed the protocol to consider pregnancy complications that require hospitalization (e.g., preeclampsia, diabetes, chorioamnionitis etc.) an SAE. The exception will be hospitalization for premature labor, which will be reported but not considered an SAE.*

7.1.3 Collection and Reporting of Specific Pregnancy Complications

Studies 17P-CT-002 and 17P-IF-001

Table 15 below demonstrates that there were numerical differences between the treatment and vehicle arms with three pregnancy complications in the principal study 17P-CT-002 and the initial formulation study 17P-IF-001 studies:

- There was a small numerical increase in the percentage of subjects with gestational diabetes in the 17-HPC arm in the principal study. In the initial formulation study (IF-001), there

were eight cases of gestational diabetes in the 17-HPC arm compared to no cases in the vehicle arm. This difference approached statistical significance.

- There was almost a three-fold increase in the percentage of subjects with oligohydramnios in the 17-HPC arm of the principal study although the actual percent difference was small (3.6% vs. 1.3%).
- The percentage of subjects with preeclampsia in the 17-HPC arm in the principal study was almost twice that in the vehicle arm. The percentage of subjects with preeclampsia in the 17-HPC arm in the initial formulation study was also higher.

Table 15 Selected Pregnancy Complications: Studies 17P-CT-002 and 17P-IF-001

Pregnancy Complication	Study	17-HPC N (%)	Vehicle N (%)
Gestational Diabetes	CT- 002	17 (5.6)	7 (4.6)
	IF- 001	8 (8.6)	0 (0.0)
Oligohydramnios	CT- 002	11 (3.6)	2 (1.3)
	IF- 001	2 (2.2)	1 (1.9)
Preeclampsia	CT- 002	27 (8.8)	7 (4.6)
	IF- 001	6 (6.5)	2 (3.8)

Source: Adapted from table 12-3 Final Report for Study 17-CT-002.

New Protocol

The Applicant proposes to collect and report data on the following complications of pregnancy:

• *Gestational diabetes*: Any degree of glucose intolerance with onset or first recognition during pregnancy. A fasting plasma glucose level > 126 mg/dL (7.0 mmol/L) or casual plasma glucose > 200 mg/dL (11.1 mmol/L) meets the threshold for the diagnosis of diabetes, if confirmed on a subsequent day, and precludes the need for any glucose challenge.

• *Oligohydramnios*: Amniotic fluid index < 2 cm or, when using a 4-quadrant method, a sum of < 5 cm.

• *Significant antepartum bleeding or hemorrhage*: Bleeding after the subject was randomized, including that resulting from placenta previa, placental abruption, or threatened abortion. Spotting is not considered significant.

• *Preeclampsia*: Having two blood pressure measurements = 140/90 mmHg on at least two occasions (four or more hours apart) and a clinical diagnosis of preeclampsia, eclampsia, or HELLP syndrome.

• *Gestational hypertension*: Having two blood pressure measurements = 140/90 mmHg on at least two occasions (four or more hours apart) and a clinical diagnosis of gestational hypertension.

• *Abruption*: Clinical diagnosis of placental abruption (retro-placental hematoma). Does not include abruption diagnosed solely by pathologist's report.

• *Chorioamnionitis*: Clinical diagnosis of chorioamnionitis and body temperature of >100ºF (37.8ºC) and no other defined infection. Does not include chorioamnionitis diagnosed only by a placental pathology report.

The percentage of subjects with pregnancy complications including gestational diabetes, oligohydramnios, significant antepartum bleeding or hemorrhage, preeclampsia, gestational hypertension, abruption and chorioamnionitis will be presented and compared between treatment groups using the Cochran-Mantel-Haenszel test stratified by gestational age at randomization.

Medical Officer's Comment:

- *In studies 17P-CT-002 and 17P-IF-001 there was a suggestion that 17-HPC may impair glucose tolerance, requiring further study; also, based on trends in these two studies, there is reason to study further the effects of 17-HPC on amniotic fluid levels and rate of preeclampsia..*

7.1.4 Post-Approval Developmental Assessment of Children at Ages 18-24 Months

The Division stated in the 20 October 2006 Approvable Letter the following additional issues that would need to be addressed postmarketing, if the product were to be approved:

- *Long-term post treatment safety data (at least through puberty) from children whose mothers had been treated with HPC is lacking in the NDA. This information is requested and could be obtained through the establishment of a surveillance program (e.g., registry) to evaluate the effects of prenatal exposure in adolescents and young adults. Submit your proposal as to how these data would be obtained.*
- *Additional developmental assessment is needed of children at ages 18-24 months whose mothers had been treated with HPC. This assessment could be obtained from the offspring of women enrolled in the confirmatory efficacy study or the safety study addressing early fetal loss. Children who screen positive for developmental delay should have a formal psychometric assessment and an additional assessment by a neurologist.*

Development Assessment of Children at Ages 18-24 Months

As part of the phase 4 commitments, Cytyc proposes to conduct a follow-up study of children born to mothers who complete the proposed efficacy and safety trial. The objective of this follow-up study will be to determine whether there are differences in the achievement of developmental milestones between children whose mothers received 17-HPC and those who received vehicle only. In determining whether developmental differences exist between the two groups, subjects will initially be screened for developmental delay using the Ages and Stages Questionnaire (ASQ). Subjects who test positive for delay in any one of the five ASQ domains will be referred for a secondary assessment of the child's performance in the area(s) for which they screened positive (e.g., Bayley Scales of Infant and Toddler Development, neurological exam, Gross Motor Function Classification System, Modified Checklist of Autism in Toddlers). A completed ASQ will be obtained for approximately 375 children (250 17-HPC and 125 placebo), requiring an estimated 500 children to be enrolled initially.

The final protocol for the Infant Follow-Up Study will be submitted to the Division for review in the next cycle and the study would be conducted as a phase 4 commitment.

Primary Objective

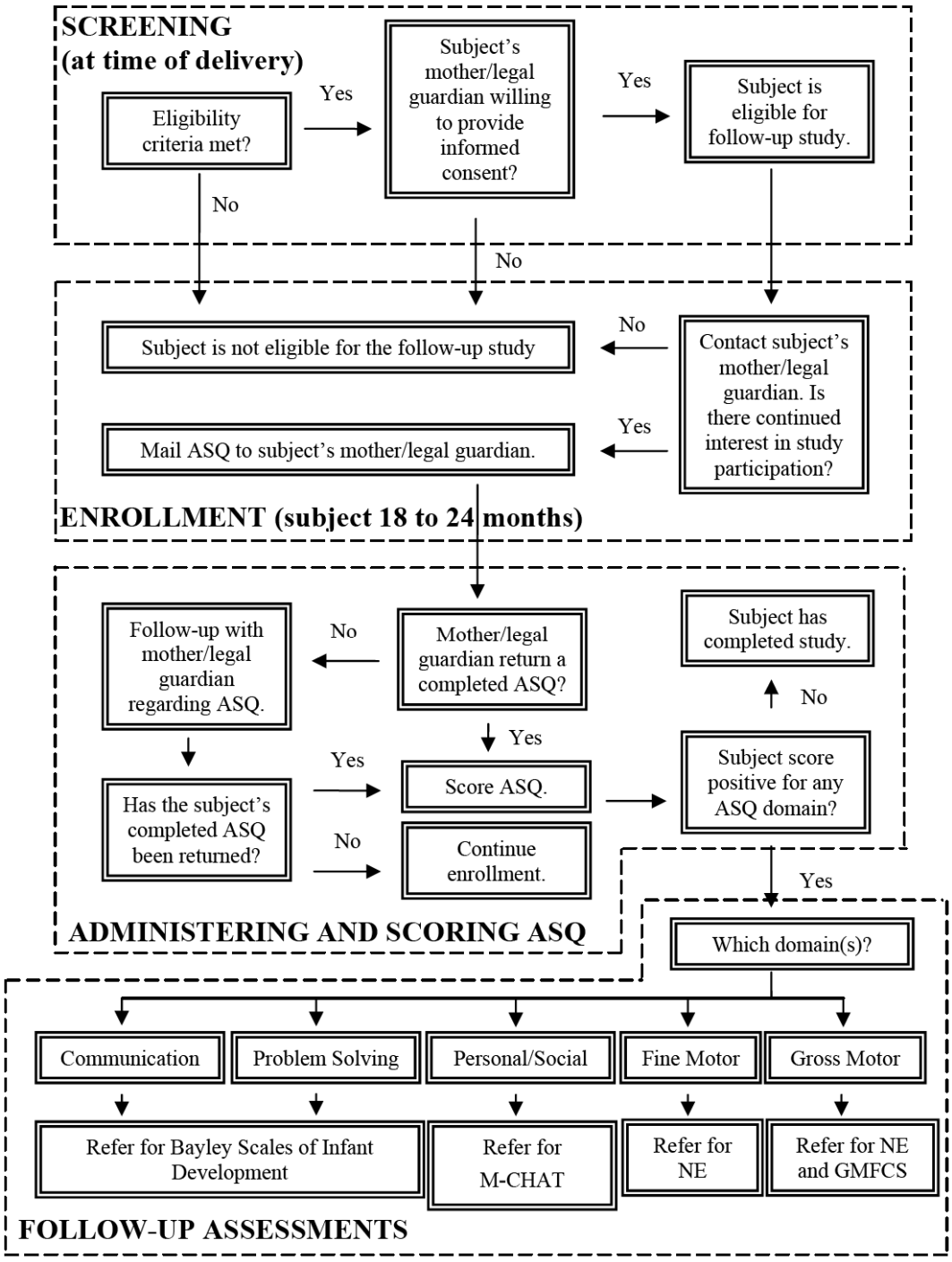
The primary objective of this study is to determine whether there is a difference in the achievement of developmental milestones between children aged 18 to 24 months whose mothers received 17-HPC and those who received vehicle in the confirmatory efficacy trial.

Overall Design

This will be a prospective, non-interventional follow-up study designed to provide a developmental assessment of children born to mothers who participated in the confirmatory efficacy trial. Subjects will be screened for developmental delay using the ASQ. Subjects who screen positive for developmental delay in one or more domain will be referred for an appropriate secondary assessment based on the domain(s) for which the subject scored positive.

Participating women will initially be asked to consent to future contact for the purpose of an infant follow-up study. Mothers/legal guardians (hereafter referred to as mothers) will be contacted periodically until the subject reaches the enrollment age to confirm that their contact information is current. When subjects near the minimum enrollment age the subject's mother will be contacted to review the study and describe the ASQ. Once their continued interest in participating has been ascertained, the ASQ will be mailed to the subject's mother and she will be asked to return the ASQ upon completion. The mothers of subjects who screen positive for any one of the five ASQ domains will be contacted regarding a referral for an appropriate follow-up for the child. The purpose of the follow-up will be to provide a secondary assessment of the child's performance in the area(s) one which they screened positive. Completed ASQs will be obtained from 375 subjects. The conduct of the study is presented diagrammatically in Figure 2.

Figure 2 Overview of Study Conduct



Abbreviations: ASQ, Ages and Stages Questionnaire; GMFCS, Gross Motor Function Classification System; M-CHAT,
Modified Checklist for Autism in Toddlers; NE, neurological exam.
Source 24 April 2008 Complete Response Section 5-1 Draft Infant Follow-up Study Protocol P 11

Primary Outcome

The primary outcome will be the proportion of children who fall below the specified cutoff (see Appendix A: Cutoff Scores by Interval and ASQ Domain) for at least one of the developmental areas. For each area, a score will be determined as the sum of the score for each question in that area. Each question will be scored as YES=10, SOMETIMES=5 and NOT YET=0. If a question has not been answered, then a value equal to the mean of the scores for the questions answered within that developmental area will be used. If more than two questions within a developmental area have not been answered, the entire developmental area will be considered missing and the primary outcome will be determined from the non-missing developmental areas.

Secondary Outcomes:

• ASQ score by developmental area – the proportion of children who fall below the specified cutoff for *each* of the developmental areas: communication, gross motor, fine motor, problem solving, and personal/social.

• Secondary assessments - Children who screen positive for any one of the five ASQ domains will be referred for an appropriate secondary assessment(s) based on the domain(s) for which they screened positive. The outcomes measures below indicated as "under development" will be finalized and submitted in a final protocol to the Division for review before the study is initiated.

- Bayley Scales of Infant and Toddler Development
  - Motor Scale – definition of outcome measure [under development].
  - Mental Scale – definition of outcome measure [under development].
  - Behavior Rating Scale – definition of outcome measure [under development].
- Neurological Exam – definition of outcome measure(s) [under development].
- Gross Motor Function Classification System – the proportion of children within each classification level.
- Modified Checklist for Autism in Toddlers – the proportion of children who fail the checklist. A failure is defined as failing two or more critical items on the checklist or any 3 items on the checklist.

Subject Enrollment

Subjects enrolled in the study will be children whose mothers participated in the confirmatory efficacy trial. *Subjects will be enrolled until at least 375 completed ASQs are obtained. Approximately 450 to 500 children are expected to be enrolled to reach 375 completed ASQs.* A subject will be considered enrolled once the ASQ has been mailed to their mother/legal guardian.

Medical Officer's Comment:

On January 8, 2009, the following requests regarding subject enrollment were sent to the Applicant:

- *Obtain consent from all women who enter the trial to be recontacted and asked for consent for their child to be evaluated in the infant/toddler follow-up study. Actual enrollment of exposed off-spring would entail a second consent process; this initial consent to be recontacted would simply notify women of the planned additional study and ensure that adequate contact information was obtained to allow tracking of the participants several years after conclusion of the maternal trial. Women who decline would still be eligible to*

participate in the pregnancy study; however, the Applicant would need to ensure that sufficient numbers who are agreeable to participating in the follow-up study are enrolled in each arm. The applicant agreed to this in the revised protocol sent January 15, 2009.

- *The final number/percent of subjects to be enrolled in the infant/toddler study will be negotiated during the next cycle when the protocol (development of outcome measures) for that study is completed.*
- *Women should remain blinded to the treatment/study group they were assigned to until after the completion of the infant/toddler study.*

Inclusion Criteria
Each subject must meet the following criteria to be enrolled in this study:

1) Maternal enrollment in the Multi-center, Randomized, Double-blind Study of 17 α-Hydroxyprogesterone Caproate (17-HPC) Versus Placebo for the Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery.
2) Children between 18 and 24 months of age, based on corrected gestational age.

Medical Officer's Comment:
At age 18 to 24 months, most cases of cerebral palsy and mental retardation can be identified by appropriate assessments.

Exclusion Criteria
Subjects meeting any of the following criteria will be excluded from the study:
1) There is no parent/guardian available to sign an informed consent.
2) Born to women who were unblinded to study group assignment.

Subject Withdrawal
The investigator may withdraw a subject from the study if:
1) The subject's mother is made aware of the mother's treatment assignment.
2) The subject's mother fails to comply with the study protocol.

Enrollment (No Visit Required)
Once the subject's mother has been contacted and continued interest in the study is ascertained, the ASQ will be described and any questions answered. When all questions about participation have been answered, the ASQ will be mailed to the mother with instructions for completing and returning the questionnaire. A subject will be considered enrolled in the study when the ASQ has been mailed to the subject's mother.

The subject's mother will complete the ASQ appropriate for their child's age. Instructions for completing the ASQ will be provided. Once the ASQ is completed the subject's mother will return the ASQ for scoring.

Medical Officer's Comment:

- (b) (4) *, was consulted because of her expertise in developmental pediatrics. She made the following comment regarding the previous study 17P-FU: "The major weakness of the study is that the data was primarily*

dependent on parental report. Although the ASQ is an excellent screening tool, it is meant to be combined with other strategies as part of a comprehensive follow-up of at-risk infants." As stated below, infants with a positive ASQ score in more than one domain will be further evaluated. How the Applicant will put this plan into operation will need further delineation.

Follow-Up Assessments (Visits Required As Necessary)

Subjects who screen positive on any one of the five ASQ domains will be referred for appropriate additional testing specific to the domain(s) for which they scored positive for. *If a subject screens positive in more than 1 ASQ domain, all domains of concern* (i.e., domains for which the subject screened positive) *will be evaluated*. Table 16 lists appropriate secondary assessments for each of the 5 ASQ domains.

Table 16 Appropriate Secondary Assessments for Each of the ASQ Domains

ASQ Domain (Area of Development)	Secondary Assessment
Communication	Bayley Scales of Infant Development- 3rd Ed
Problem Solving	Bayley Scales of Infant Development- 3rd Ed
Personal/Social	M-CHAT
Fine Motor	Neurological Exam
Gross Motor	Neurological Exam and GMFCS

Abbreviations: ASQ, Ages and Stages Questionnaire; GMFCS, Gross Motor Function Classification System; M-CHAT, Modified Checklist for Autism in Toddlers

Study Assessments

Demographic Data/Baseline Characteristics

Data concerning subject demographics and baseline characteristics (e.g., gestational age at birth, birthweight, Apgar score and morbidities at birth) will be obtained from the CRFs of the confirmatory efficacy trial.

Ages and Stages Questionnaire

The ASQ screening system is composed of 19 questionnaires, each corresponding to a specific age between four months and five years and each containing 300 developmental items addressing five areas: communication, gross motor, fine motor, problem solving, and personal/social. The questionnaires are designed to identify young children who are in need of further evaluation and early intervention services. The ASQ recommends using gestationally corrected age until 24 months. The ASQ has been validated against professionally administered assessments, such as the Bayley Scales of Infant Development and the McCarthy Scales of Children's ability. Overall agreement for identifying children with delay ranged from 76% to 91%. The ASQ uses cut-off points to determine whether a child's score on the questionnaire indicates that the child should be referred for an in-depth evaluation. The cut-off points were generated for each area of development, and in general correspond to two standard deviations below the mean. The cut-offs by age and area of development are provided in Appendix A: Cutoff Scores by Interval and ASQ Domain

Follow-Up Assessments

Bayley Scales of Infant and Toddler Development-3rd Edition

The Bayley Scales of Infant and Toddler Development (3rd Edition) is a standard assessment used to evaluate skills in infants and toddlers, ages 0 to 3 years. The Bayley Scales is an individually administered assessment composed of a series of developmental play tasks used to provide an evaluation of a child's performance in three domains (Scales): Motor Scale, Mental Scale, and Behavior Rating Scale. The Motor Scale measures fine and gross motor control through the performance of general activities such as sitting, running, reaching and grasping; the Mental Scale assesses cognitive development through memory, language, imitation and problem solving; and the Behavior Rating Scale evaluates the child's qualitative behaviors displayed during the completion of the other two scales.

Medical Officer's Comment:

This follow-up assessment is critical. In an evaluation of the ASQ, (Skellern 2001[55]) found that the ASQ agreed with standard psychometric tests 67% when assessing 14 children with known disabilities. The formal evaluation of screen-positive children by an age-appropriate standard psychometric test will strengthen the findings.

Neurological Exam

A standard neurological assessment appropriate for the subject's age will be performed by a neurologist. The components of the neurological assessment are under development by the Applicant.

Medical Officer's Comment:

An assessment of neurologic status by either a neurologist or developmental pediatrician is a critical component of this study.

Gross Motor Function Classification System (GMFCS)

The Gross Motor Function Classification System was designed to classify gross motor function in children with cerebral palsy. The system is based on a five-level classification system where distinctions between levels are defined by clinically significant observations, meaningful to daily life. Distinctions are based on functional impairment, and, within each of the five levels, descriptions are provided for several age bands. It is recommended that gestational age-corrected age be used for children below the age of 2 if they were born premature.

Modified Checklist for Autism in Toddlers (M-CHAT)

Autistic disorder comprises impairment in three areas: reciprocal social interaction, communication, and particular patterns of behavior, interests and activities. With regard to autistic disorders, several screening tools have been created and continue to be revised. The M-CHAT is one such screening tool; an expanded version of the Checklist for Autism in Toddlers (CHAT). Where the CHAT was originally designed to screen children strictly for autistic disorder, the M-CHAT expands upon the parent report, assisting in identifying children with a possible autistic spectrum disorder. The M-CHAT is composed of 23 items and was developed to be used with children 16 to 30 months of age.

Statistical Methods

Sample Size

A completed ASQ will be obtained for a minimum of 375 children (250 17-HPC and 125 placebo subjects). The NICHD Follow-Up study enrolled 278 children (194 17-HPC and 84 placebo subjects) and found 28% of children fell below the specified cutoff for at least one developmental area on the ASQ. The sample size for the current study was based on enrolling a similar number of children as in the NICHD Follow-Up study, as well as providing a sufficient power to detect a two-fold increase in the 17-HPC group in the proportion of children with the primary outcome. Assuming a completed ASQ is obtained for 250 17-HPC and 125 placebo subjects, there is an 88% power to detect a 15% absolute difference, using an alpha level of 0.05 and an outcome rate of 30% in the 17-HPC group.

Medical Officer's Comment:

- *As stated previously the number/percent of subjects to be enrolled in the infant/toddler study will be negotiated during the next cycle when the protocol (development of outcome measures) for that study is completed*.

Population to be Analyzed

One population will be analyzed; all subjects with a completed ASQ.

Statistical Methodology

Inferential statistical analyses will be conducted and all comparisons will be between the 17-HPC and vehicle groups. An alpha level of 0.05 will be used for all analyses. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums and maximums for continuous variables will be provided. Listings of individual subjects' data will also be provided. A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized prior to database lock and analysis of the data.

Subject Disposition

A summary of subject disposition will be provided. Specifically, the number of mothers providing informed consent, the number of subjects enrolled in the study and the primary reason a subject was not enrolled in the study will be provided by treatment group. In addition, the number of subjects withdrawn from the study and the reason for withdrawal will be summarized by treatment group.

Subject Population and Characteristics

Neonatal data for subjects enrolled in the study will be presented. Descriptive statistics of the gestational age at delivery, birth weight, head circumference and 1 and 5 minute Apgar scores will be provided. The percentage of subjects with selected neonatal morbidities such as transient tachypnea, respiratory distress, bronchopulmonary dysplasia, persistent pulmonary hypertension, patent ductus arteriosus, seizures, intraventricular hemorrhage, retinopathy of prematurity, sepsis and necrotizing enterocolitis will be provided. The demographics of the subjects will be presented including age at enrollment, sex and race/ethnicity. Difference between treatment

groups will be analyzed using the chi-square or Fisher's exact test for dichotomous variables and the Wilcoxon Rank Sum test for ordinal and continuous variables.

Primary Outcome
The percentage of children who fall below the specified cutoff for at least one of the developmental areas will be summarized by treatment group. Differences between treatment groups will be analyzed using the chi-square test, or if the expected number of children above or below the cutoff in either treatment group is 5 or less, Fisher's exact test will be used.

The percentage of children who completed each age interval questionnaire, the child's age at the time the questionnaire was completed, and who completed the majority of the questionnaire will also be presented.

Secondary Outcomes
ASQ
The percentage of children who fall below the specified cutoff for each of the developmental areas (communication, gross motor, fine motor, problem solving, and personal/social) will be summarized by treatment group for all subjects with a completed ASQ. Differences between treatment groups will be analyzed using the chi-square or if the expected number of subjects above or below the cutoff in either treatment group is 5 or less, Fisher's exact test will be used.

Bayley Scales of Infant and Toddler Development
Under development.

Neurological Exam
Under development.

Gross Motor Function Classification System
The percentage of children classified to each level will be summarized by treatment group. Differences between treatment groups will be determined using the Wilcoxon Rank Sum test.

Modified Checklist of Autism in Toddlers
The percentage of children who fail the checklist will be summarized by treatment group. Differences between treatment groups will be analyzed using the chi-square, or if the expected number of children above or below the cutoff in either treatment group is 5 or less, Fisher's exact test will be used.

Monitoring of the Study
All aspects of the study will be carefully monitored by the Applicant or its designee, for compliance with applicable government regulations with respect to current GCP and current standard operating procedures. Investigators and institutions involved in the study will permit trial-related monitoring, audits, Internal Review Board/Internal Ethics Committee (IRB/IEC) review, and regulatory inspection(s) by providing direct access to all study records. Essential documents will be retained until at least 2 years have elapsed since the formal discontinuation of clinical development of 17-HPC.

Medical Officer Comments:

- *This proposal for the infant follow-up study is not yet complete; however, the draft appears to be a significant improvement from the previous study. Specific improvements include:*
    - *A formal evaluation by an age-appropriate standard psychometric test.*
    - *An assessment of neurologic status by a neurologist.*
- *The review of the final protocol will occur in the next cycle. The two major outstanding issues are:*
    - *Completion of outcome measures.*
    - *Review by statisticians.*

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal Effects

17-HPC is to be administered weekly from 16^0 until 36^6 weeks of gestation. Nothing in the clinical studies would suggest a safety risk if 17-HPC treatment is withdrawn after initiation of treatment, other than the possible outcome of a preterm delivery, which the drug is intended to prevent.

Data from women who received 17-HPC as outpatients in Matria Healthcare services between January 2004 and May 2006 were retrospectively analyzed for early withdrawal effects (Rebarber 2007b [56]). The dataset included 481 women with previous preterm delivery and current singleton pregnancy who began weekly 17-HPC injections (250 mg intramuscularly) at 16^0-20^6 weeks of gestation. Of the 481 women, 81 (16.8%) were identified as having early discontinuation of 17-HPC treatment at <32 weeks of gestation and delivery occurring >10 days from the last injection. Women with early cessation of 17-HPC were more likely to be teenagers (8.6% vs. 1.8% <20 years), unmarried (45.7% vs. 27.0%), cigarette smokers (12.3% vs. 5.8%), and to have >1 previous preterm birth (34.6% vs. 23.5%). Of the 81 women who discontinued 17-HPC early, 51 (63.0%) experienced spontaneous or indicated preterm delivery compared with 164 of the 400 (41.0%) of those who continued 17-HPC injections per protocol (p<.001). Because of the significant differences in maternal characteristics between the 2 groups, a logistic regression model was used. *The full model results in this study suggested that elective early cessation of 17-HPC injections carries twice the risk of spontaneous recurrent preterm birth at <37 weeks of gestation.* This retrospective exploration of data, however, has methodological flaws, because the length of therapy is tied to outcome (i.e., a preterm delivery <37 weeks cannot be observed in a patient who received therapy up to 37 weeks). There is an inherent bias towards term delivery in the group of patients getting therapy up to 37 weeks, and therefore, the effect of cessation of therapy is difficult to study retrospectively. In addition, Bernstein (2008) in a letter to the editor questioned the data interpretation by Rebarber and colleagues [56], suggesting the possibility that many patients in this retrospective study may have received medication in ways and for indications for which 17-HPC has not been shown effective.

7.1.14 Human Reproduction and Pregnancy Data

Refer to Section 8.7

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.2 Postmarketing experience (AERS Reports)

Spontaneous Adverse event Reports submitted to the FDA

The spontaneous reporting system (AERS) maintained by the Food and Drug Administration (FDA) contains spontaneously reported adverse events (AEs) that have been reported by health care providers or laypersons either directly to the FDA or to the FDA via the manufacturer.

The Division of Reproductive & Urologic Products (DRUP) previously requested in 2006 that the Division of Drug Risk Evaluation (DDRE) review any adverse event reports related to compounded preparations of 17α-hydroxyprogesterone caproate received from June 2003 to August 2006. The June 2003 start date was chosen to coincide with the publication date of study 17P-CT-002 regarding 17-HPC use to prevent recurrent pre-term birth.[1] Following publication of that study, physicians began prescribing the drug for pre-term labor prevention. DRUP has requested an update from the Division of Pharmacovigilance II (DPV II) of any adverse event reports received since the previous review.

The Adverse Event Reporting System (AERS) was searched on 5/27/2008 with 17-HPC as a suspect drug for all reports received by the FDA without regard to a received date. There were nine unique cases, three were discussed in the previous review. Therefore, there are six unique cases that were received from 8/16/2006 until 5/27/2008. Of these six cases, five were reported from a study evaluating the pharmacokinetics of 17-HPC in women receiving the drug for therapeutic purposes (IND 72,283; principal investigators Steve N. Caritis, M.D., Pittsburgh, PA [1 case] and Mary F. Hebert, Pharm.D., Seattle, WA [4 cases]). The following is a list with a summary prepared by DDRE of the reported cases:

AERS ISR # 5281471-8—A 36 year old female at 33 1/7 weeks gestation was admitted to the hospital after a syncopal episode with loss of consciousness for two to three minutes. She has had previous episodes of intermittent diaphoresis/palpitations and a history of pre-syncope since a gastric bypass surgery. The patient was discharged after two days with no further episodes.

AERS ISR # 5218355-7—A 24 year old gravida 5, para 1 (2), female presented at her normal appointment with frequent contractions (gestational age 32 4/7 weeks). She was admitted for observation and started on nifedipine and received a course of betamethasone. The patient was discharged after three days as her contractions had stabilized.

AERS ISR # 5311445-X—A 32 year old gravida 3, para 1 (0), female presented at her regular appointment and was found on ultrasound to be 2 cm dilated with funneling to the external os (gestational age 24 0/7 weeks). She was admitted and received a rescue cerclage. She was placed on tocolytic ibuprofen therapy and, at the time of the report, was being monitored with a plan to discharge if her cervical length remained stable.

AERS ISR # 5154721-6—A 37 year old gravida 2, para 2, female presented at 28 6/7 weeks gestation with preterm labor. She was completely dilated with bulging membranes. A male infant was delivered by an uncomplicated standard vaginal delivery. The baby was diagnosed with respiratory distress syndrome and was admitted to the NICU in critical condition on respiratory support because of extreme pulmonary immaturity. He is also on phototherapy for jaundice.

AERS ISR # 5272646-2—A 28 year old gravida 6, para 0 (5), female who was approximately 24 weeks gestation was admitted to the hospital for depression**,** paranoia, anxiety, and suicidal ideation. The subject has a history significant for rapid cycling bipolar disorder and bulimia, with a strong family history of mental illness. She had not been on psychiatric medication for four years prior to this event. She had received two doses of 17-HPC and the events occurred five weeks after the second dose. She had not kept her scheduled appointments for follow-up injections. The patient later admitted that she was not truly feeling suicidal but used those statements because she knew that would result in her hospitalization. She was discharged after four days in stable condition.

The sixth case (AERS ISR # 5143070-8) was reported by a patient who had received 17-HPC during her pregnancy for 16 weeks and gave birth to a female infant with a congenital heart defect who subsequently died at six days of age.

DDRE made the following conclusions and recommendation:
"Of the six new cases, three were related to preterm labor and, as such, could not be considered an adverse event of the drug. No definitive conclusions can be drawn from the single report each of syncope, depression, and congenital heart defect. The patient who experienced syncope had a previous history of pre-syncopal episodes, and the patient who experienced psychiatric events had a significant personal and family history of mental illness. Congenital heart defects are the most common type of birth defect, affecting 8 of every 1,000 newborns.[3] There is considerable evidence that favors 17α-hydroxyprogesterone caproate not being associated with birth defects.[4-8] In addition, most congenital heart defects occur from errors early in the heart's development, which occurs well before the currently recommended use of the drug. DDRE will continue to monitor reports for 17α-hydroxyprogesterone caproate to determine if there are any changes."

Medical Officer's Comments

- *This reviewer agrees with the DDRE conclusions.*

7.2.3 Safety Literature

Cytyc had no ongoing 17-HPC clinical studies at the time of the NDA 21-945 submission and has conducted no new 17-HPC clinical trials. Therefore, this safety update consists of a review of published articles for safety issues related to the use of 17-HPC during pregnancy. This Safety Update provides a summary of safety information published or received by the FDA after February 2006.

Literature Based Safety Update

A review of literature published after January 2006 did not identify any new safety concern related to the use of 17-HPC for the prevention of recurrent spontaneous preterm birth.

Miscarriage/Stillbirths/Neonatal Deaths

On March 5, 2008, the FDA received the final report for the NICHD MFMU Network trial, *A Randomized trial of 17 Alpha-Hydroxyprogesterone Caproate for Prevention of Preterm Birth in Multifetal Gestation.*[7] In this trial, *795 subjects* (women pregnant with twins/triplets) were randomized 1:1 to receive weekly injections of 17-HPC or placebo, with a primary endpoint to assess the decrease in deliveries less than 35 weeks gestation.

Data on early fetal and neonatal loss are presented in Table 17. In subjects with a *twin gestation* there was a total of 16 fetal losses out of 11 pregnancies and also a total of 16 neonatal deaths out of 11 pregnancies (145%), resulting in no net survival benefit (losses from abortion/selective reduction are not included in the table). However, there was no significant difference in the percent of fetal loss in the treatment group (145%) compared to the placebo group (137%). The numbers for triplets were very small.

Table 17 Early Fetal and Neonatal Losses in NICHD Multifetal Trial

Fetal	17-HPC # pregnancies affected (# fetuses/neonates affected)	Placebo # pregnancies affected (# fetuses/neonates affected)
	Twins	
Miscarriage (<20 weeks)*	**1 (1)**	**3 (5)**
Antepartum stillbirth (~20 weeks)	**6 (8)**	**5 (6)**
Intrapartum stillbirth	**4 (7)**	**0**
Total fetal loss	**11 (16) – 145%**	**8 (11) – 137%**
	Triplets	
Miscarriage (<20 weeks)	**0**	**0**
Antepartum stillbirth	**1 (1)**	**2 (3)**
Intrapartum stillbirth	**0**	**1 (3)**
Total fetal loss	**1 (1) – 100%**	**3 (6) – 200%**
Infant		
	Twins	
Neonatal death	**11 (16) – 145%**	**8 (11) – 137%**
	Triplets	
Neonatal death	**4 (5) – 125%**	**2 (2) – 100%**

* one of the cases coded as a miscarriage is related to laser ablation performed for twin-to-twin transfusion syndrome at less than 20 week of gestation

On March 10, 2008, the FDA received the final report for the NICHD MFMU Network trial, *A Randomized Trial of Omega-3 Fatty Acid Supplementation to Prevent Preterm Birth in Pregnancies at High Risk* [57](History of previous PTB). A total of *852 subjects* were randomized 1:1 to receive Omega-3 fatty acids (FA) supplements or placebo; both arms received weekly

injections of 17-HPC. In each arm there were two miscarriages, three antepartum stillbirths, and one intrapartum stillbirth. There were nine neonatal deaths in the Omega 3 FA arm and 10 neonatal deaths in the placebo arm. See Table 18.

Table 18 IND [redacted] (b) (4) Omega-3 Fatty Acid Trial Fetal/Neonatal Deaths

Pregnancy/Neonatal Losses	Omega-3	Placebo
Miscarriage (<20 weeks)	2	2
Antepartum Stillbirth	3	3
Intrapartum Stillbirth	1	1
Neonatal Death/pre-viable delivery	9	10

Medical Officer's Comments:

- *Similar to study 17P-CT-002, there was no net survival benefit in either of these MFMU Network studies.*
- *Neither study was powered to show non-inferiority to placebo with respect to the safety endpoint of fetal/neonatal loss.*
- *It is interesting to note that there was a numerically lower percentage of miscarriages or stillbirths overall in the Omega 3 FA trial (6/852=0.7%) compared to the multifetal gestation trial(12/795=1.5%).*

Role of Infection

A mouse model of localized intrauterine inflammation was used to investigate the ability of progestational agents to prevent preterm birth (Elovitz 2004 [58]). In mice with intrauterine exposure to E. coli lipopolysaccharide (LPS), 17-HPC *decreased the rate of preterm delivery* compared with LPS treatment alone. However, treatment with 17-HPC was *associated with significant maternal morbidity.* A 4-mg dose of 17-HPC before an intrauterine LPS exposure resulted in significant maternal morbidity (piloerection, lethargy, moribund requiring euthanasia) and death for the dams. At half the dose (2 mg) maternal morbidity was present in 50% of dams. Based on these results in mice, the authors, and later Romero (2007[42]), raised concern that patients suspected of having a subclinical infection should not be given 17-HPC.

Medical Officer's Comment:

- *It is established that a significant number of women who deliver preterm have subclinical chorionic infection (Goldenberg 2002 [20]). Is there a relationship between 17-HPC, subclinical chorionic infection and stillbirth/miscarriage, or pre-viable delivery? These data provide further support that further quantitative and qualitative study is needed to assess the rates and causes of fetal and neonatal death.*

Retrospective Study

Gonzalez-Quintero and colleagues conducted a *retrospective review of a Matria Healthcare* database to examine perinatal mortality and outcomes of pregnancies exposed to 17-HPC for prevention of recurrent preterm birth (Gonzalez-Quintero 2007a[11]). Included were women with prior preterm birth and current singleton gestation, who were seen between 16.0 between 19.9 weeks of gestation for weekly injections of 17-HPC (250 mg) (n=699) or preterm labor

surveillance services (n=880). *The authors reported a miscarriage rate at < 20 weeks of gestation of 2.3% (16/699) in the 17-HPC group compared to 0.3% (3/880) in the placebo group (p=0.001; odds ratio [95% CI]: 6.8 [2.0-23.6]). However, the miscarriage rate at < 24 weeks of gestation (4.0% vs. 3.8%; p=0.794) and the total perinatal death rate (4.9% vs. 4.4%; p=0.718) were not different between the treatment groups.*

Medical Officer's Comments:

- *The limitations of this retrospective study are that no demographic information was provided on the two groups and, that as a non- randomized study, no information was provided on how women were selected to receive 17-HPC.*
- *The fetal loss rate <24 weeks was comparable to control, but the study suggested an increase in the miscarriage rate at <20 weeks of gestation in the 17-HPC arm.*
-

Gestational Diabetes

In Study 17P-CT-002, the incidence of pregnancy complications was similar for patients in the 17-HPC and placebo groups. The incidences of gestational diabetes, oligohydramnios, significant antepartum bleeding, preeclampsia or gestational hypertension, abruption, confirmed clinical chorioamnionitis, or cerclage placement were not significantly different (p>0.05) between the 17-HPC and placebo groups. The incidence of gestational diabetes was 5.6% in the 17-HPC group compared to 4.6% in the vehicle group (p=0.6674). When the data from the terminated Study 17P-IF-001 were included the rate of gestational diabetes was 8.6% in the 17-HPC group compared to 0% in the vehicle group (p=0.1792).

Rebarber and colleagues explored the question of gestational diabetes and 17-HPC using the Matria Healthcare database (Rebarber 2007a[12]). The incidence of gestational diabetes was 12.9% in the 17-HPC group compared with 4.9% in the control group (p<0.001; odds ratio [OR] 2.9; 95% CI: 2.1-4.1). Based on a logistic regression model analysis, they reported that *although obese and overweight patients had the highest risk of developing gestational diabetes (OR: 6.91 and 3.70, respectively), the use of 17-HPC continued to have a positive association with the incidence of gestational diabetes compared with placebo (OR: 3.09, 95% CI: 2.2-4.4).* It is important to note that their data: 1) were not from a randomized clinical trial; 2) were reviewed retrospectively and did not control for all possible confounding factors, such as ethnicity; and 3) did not include a standardized method for assessing gestational diabetes.

Medical Officer's Comments:

- *A decrease in glucose tolerance has been observed in some patients on progestin treatment.*
- *Further study is needed evaluate the use of 17-HPC in pre-diabetic and diabetic patients*

Congenital Anomalies

The teratogenic potential of 17-HPC, as administered to pregnant women in Hungary, was evaluated by Dudάs and colleagues using the population-based, large dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) (Dudάs 2006 [59]). Congenital anomaly cases were selected from the HCCSCA and appropriate controls were selected from the national Birth Registry of the Central Statistical Office for the HCCSCA. Controls were defined as newborn infants without congenital anomalies who matched the sex, birth week in the year

when the case was born, and the district of parents' residence. Exposure data was obtained from: 1) prenatal care logbooks and other medical records, primarily discharge summaries; 2) self-reported maternal information collected retrospectively via a structured questionnaire; and 3) data collected by regional nurses who visited all non-responding case and control mothers. Maternal age, birth order, acute and chronic maternal disorders, the use of other drugs and pregnancy supplements were evaluated as potential confounding factors. The occurrence of 17-HPC treatment during pregnancy was compared between case and control groups and crude prevalence odds ratios (ORs) with 95% confidence intervals (CI) were calculated.

Between 1980 and 1996, 22,865 fetuses and newborn infants in Hungary had congenital anomalies, of which 318 (1.4%) had been exposed to 17-HPC in utero, of whom 83 (0.36%) were exposed during the second and/or third gestational month. The total number of births in Hungary during the time period under study was 2,146,574, from which 38,151 (1.8%) were selected as controls. Of these 38,151 controls, 433 (1.1%) had mothers with 17-HPC treatment during the pregnancy, of whom 178 (0.47%) were treated during the second and/or third gestational months. 17-HPC (Hormofort®) was administered daily at 125 – 250 mg parenterally for the treatment of repeated and threatened spontaneous abortions, and threatened preterm delivery. The mean duration of treatment with 17-HPC was 6.2 weeks. Of the exposed women, 318 case and 433 control mothers, 290 (91.2%) and 396 (91.5%), respectively, had 17-HPC treatments in prenatal care logbooks and/or discharge summaries.

No association was found between any type of congenital anomaly and 17-HPC treatment given during the second and/or third month of pregnancy. When 17-HPC treatment was examined "any time during the pregnancy," a difference was seen in the limb deficiency group compared to the matched control group. However, this finding was not replicated in the 17-HPC treatment period of the second and/or third months, the critical period of exposure for major congenital anomalies. This study of daily administration of 125-250 mg of 17-HPC concluded that "data did not indicate any teratogenic potential of hydroxyprogesterone [17-HPC] use during early pregnancy".

Medical Officer's Comment:

- *In 1999, the FDA conducted a thorough scientific review of the association between progesterone use and congenital malformations and concluded that no evidence existed to show any association. In a final rule published in the Federal Register on 16 November 1999, the FDA concluded that based on a review of scientific data, there is no need for class labeling of drugs containing natural progesterone or synthetic progestins to carry special labeling warning pregnant women against their use during the first trimester of pregnancy.*

7.2.9 Additional Submissions, Including Safety Update

In the Approvable Letter for 17-HPC, the Division made the standard request:
"When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.5(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration, regardless of the indication, dosage form, or dose level."

17-HPC (proposed trade name: Gestiva™), the drug product for which Cytyc is seeking FDA's approval to market, "*has not been studied or sold outside the United States (US).*" The active pharmaceutical ingredient 17 α-hydroxyprogesterone caproate (17-HPC) is being prescribed in the U.S. and produced by compounding pharmacies.

Since Cytyc had no ongoing 17-HPC clinical studies at the time of the NDA 21-945 submission and has conducted no new 17-HPC clinical trials, the specific request were not applicable. Therefore, the safety update consists of a review of published articles for safety issues related to the use of 17-HPC (produced by compounding pharmacies or other sources) during pregnancy. These articles have been discussed previously in this review.

Medical Officer's Comment:

- *One study of 17-HPC in pregnant women is currently underway in France.*

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Conclusions on Safety of 17-HPC for Use in Pregnant Women

In support of the *original application* for the use of 17-HPC for the prevention of preterm birth, the Applicant (Adeza Biomedical) submitted data from one principal active treatment clinical trial (study 17P-CT-002) and a follow-up safety analysis (study -FU).

The principal study was a double blind, vehicle controlled trial that randomized subjects 2:1 to 17-HPC or vehicle. Listed below are the overall safety results from study 17-CT-002:

- There were no *definitive* safety issues identified.
- The FDA is concerned that in Study 17-CT-002 there was a trend toward an increased risk of miscarriage and stillbirths in the 17-HPC treatment arm, and that, despite a trend toward a decrease in neonatal death, there was no net survival benefit. See Table 19

Table 19 Miscarriages, Stillbirths, and Neonatal Deaths

Pregnancy Outcome	17OHP-C N=306 n (%)	Placebo N=153 n (%)	Nominal P-value [A]
Miscarriages <20 weeks gestation	5 (1.6)	0	0.1746
Stillbirth	6 (2.0)	2 (1.3)	0.7245
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.1159
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.6887**

[A] No adjustment for multiple comparisons.
Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

- In studies 17P-CT-002 and 17P-IF-001, there was a suggestion that 17-HPC may impair glucose tolerance, warranting further study. Also based on trends, there is reason to further study the effects of 17-HPC on amniotic fluid levels and preeclampsia.

- Injection site pain, swelling and pruritus were the most common AEs and reasons for discontinuation in study 17-CT-002.

Regarding study 17P-FU:

- There were no signals of developmental delay in the limited follow-up study of children; however, this study was an "ad hoc" addition to the principal study and as such, had some deficiencies, e.g., less than optimum recruitment into the study and lack of neurologic examination in children who screened positive.

An Advisory Committee meeting was held on August 29, 2006 and made the following safety conclusions:

- "There is strong opinion that required post-marketing studies are conducted, particularly to further assess safety" (Advisory Committee for Reproductive Drugs 2006 [53]).

Several national surveys have indicated that a large number of obstetricians (at least 50%) treat pregnant women at risk of PTB with "progesterone." Some of these physicians are using compounded 17-HPC which is currently not available as an FDA-regulated, GMP-produced product, potentially introducing risks.

Selected publications (see section 7.2.3) since February 2006, with conflicting results, have shed further light on safety of 17-HPC:

Fetal/Neonatal Death

- One randomized placebo-controlled trial conducted by the NICHD MFMU Network did not show any specific trend in miscarriage or stillbirth comparing 17-HPC to placebo. An animal model (mouse) studies suggest a possible concern when using 17-HPC in preterm pregnancies with subclinical chorioamnionitis. (Final Study Report IND (b) (4)
- One retrospective review of a database revealed a fetal loss rate at <24 weeks was comparable to controls, but it there was an increased rate of miscarriage in the 17-HPC arm at <20 weeks of gestation. (Gonzalez-Quintero 2007a[11])

Diabetes in Pregnancy

- In one retrospective review of a database, 17-HPC had a positive association with the incidence of gestational diabetes compared with placebo (Rebarber 2007[12])

In an AERS search by the FDA , six new cases were discovered since October 2006; three were related to preterm labor and no definitive conclusions can be drawn from the single report each of syncope, depression, and congenital heart defect.

Plans for Future Study

Deaths (miscarriages/pre-viable infants/stillbirths)

The Applicant plans to (secondary outcomes) exclude a doubling of the risk in the 17-HPC group compared to the placebo group of the composite of:

- fetal/early infant death, defined as:
  - spontaneous abortion/miscarriage (delivery from 16^0 through 19^6 weeks of gestation) or
  - death (from minutes after birth until 28 days of life) occurring in liveborns born at less than 24 weeks gestation
- stillbirth (antepartum or intrapartum death from 20 weeks gestation through term)

Analysis of the secondary outcome of fetal/early infant death will be conducted in the ITT Population. The relative risk of fetal/early infant death for the 17P group relative to the placebo group will be determined using the Cochran-Mantel-Haenzel procedure stratified by gestational age at randomization. A two-sided 95% confidence interval (CI) for the relative risk will be constructed using the method of Cochran-Mantel-Haenzel adjusted for gestational age at randomization. If the upper bound of the CI is less than or equal to 2.0, a doubling in the risk of fetal/early infant death can be ruled out. Treatment-by-gestational age at randomization interaction terms will be included in a logistic regression model to determine the relationship, if any, between gestational age at randomization and the risk of fetal/early infant death in the 17P group compared to the placebo group.

Stillbirths/fetal deaths/in-utero fetal losses[18] will have a comprehensive worked up as recommended by the Stillbirth Collaborative Research Network of the National Institute of NICHD, to investigate the cause of death.

Pregnancy Complications

The Applicant proposes to collect and report data on the following complications of pregnancy: gestational diabetes, oligohydramnios, significant antepartum bleeding or hemorrhage, preeclampsia or gestational hypertension, abruption, and chorioamnionitis.

Infant/Toddler Follow-up

As part of the phase 4 commitments, Cytyc proposes to conduct a follow-up study of children at age 18 to 24 months (when most cases of cerebral palsy and mental retardation can be identified) born to mothers who complete the proposed efficacy and safety trial. The objective of this follow-up study will be to determine whether there are differences in the achievement of developmental milestones between children whose mothers received 17-HPC and those who received placebo. In determining whether developmental differences exist between the two groups, subjects will initially be screened for developmental delay using the Ages and Stages Questionnaire (ASQ). Subjects who test positive for delay in any of the five ASQ domains will be referred for a secondary assessment of the child's performance in the area(s) for which they screened positive (e.g., Bayley Scales of Infant and Toddler Development, Neurological Exam, Gross Motor Function Classification System, Modified Checklist of Autism in Toddlers).

As part of the phase 4 commitments, Cytyc proposed to conduct a long-term safety study to evaluate the effects 17-HPC prenatal exposure in adolescents. However, the Division informed

the Applicant that a since the reproductive toxicology study did not raise any concerns, another study to follow up children in adolescence will be requested only if findings from the infant/toddler study raises concerns about long-term safety of in-utero exposure to 17-HPC.

A final protocol for the follow-up study of children at age 18 to 24 months will be provided for agreement prior to approval.

8 ADDITIONAL CLINICAL ISSUES

8.7 Postmarketing Risk Management Plan (Phase 4 Commitment)

The combined Infant Follow-up Studies

The Infant Follow-Up Study 17P-FU submitted in the first review cycle evaluated the health status of children who were exposed in utero to 17-HPC. At the time of the follow-up, the children (194 exposed to 17-HPC; 84 to placebo) were between 2.5 and 5.4 years of age (mean age: 3.9 years). The 17P-FU Study identified no negative effect of in utero-exposure to 17-HPC. The results showed: 1) no delay in development in any of the 5 areas measured by the Ages and Stages Questionnaire (ASQ) (communication, gross motor, fine motor, problem-solving, and personal-social); 2) no safety concerns related to overall health or physical development; and 3) no association with the development of genital or reproductive anomalies.

A second Infant Follow-up Study, as requested by the Division, will be conducted on offspring from of the phase 4 efficacy and safety study for 17-HPC (discussed in Section 5.3). This study proposes to collect safety data on 375 (250 17-HPC; 125 placebo) exposed children between 18 and 24 months of age. In total, between both studies, data will be collected on approximately 450 17-HPC in utero-exposed children followed for a minimum of 18-24 months and a maximum of 5.4 years.

Medical Officer's Comments:

- *As stated previously, the number of infant/toddlers that will be enrolled in the Infant Follow-Up Study will be determined during the next cycle*.

Historical clinical data and FDA's assessment

A number of published studies have examined the effects of in utero-exposure of 17-HPC on the developing fetus, including assessments of congenital anomalies and psychological development (Varma 1982, [60] Resseguie 1985, [61] Check 1986, [62]) None of these studies identified a safety signal that would indicate an adverse effect of 17-HPC in utero-exposure. The long-term impact of in utero-exposure to 17-HPC on psychological development has also been examined. Kester (1984 [63]) examined adolescent males exposed to 17-HPC to determine whether prenatal exposure impacted recreational interests and psychosexual development in boyhood. Twenty-five males exposed to 17-HPC and closely matched unexposed controls were evaluated based on a number of psychological tests. The mean age of the subjects was 15 years (range: 12-18) in each study group. No significant differences in psychological testing were noted for adolescents exposed to

17-HPC. The total dosage of 17-HPC, duration of exposure, and period of gestation had no significant impact on the findings.

In 1999, the FDA conducted a thorough scientific review of the association between progesterone use and congenital malformations and concluded that no evidence existed to show any association. In a final rule published in the Federal Register on 16 November 1999, the FDA concluded that based on a review of scientific data, there is no need for class labeling of drugs containing natural progesterone or synthetic progestins to carry special labeling that warns pregnant women against their use during the first trimester of pregnancy.

17-HPC dosing is initiated after the first trimester, at 16 weeks of gestation, following completion of major developmental processes in the fetus.
In assessing the potential effects of steroid hormones on genital and reproductive tract abnormalities, it is important to recall that 17-HPC exposure is to be initiated during the second trimester (16^0 - 20^6 weeks of gestation), a time when the lower genital tract of the fetus has already formed. If exposure to androgens occurs after 14 weeks of gestation, vaginal development will occur normally. By 15 weeks, all of the fetus' major organs have formed.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy Conclusions

In support of the original application for the use of 17-HPC for the prevention of preterm birth, the Applicant (Adeza Biomedical) submitted data from one principal active treatment clinical trial (study 17P-CT-002) and a follow-up safety analysis (study 17P-FU). The principal study was a double blind, vehicle controlled trial that randomized subjects 2:1 to 17-HPC or vehicle. Inclusion criteria were pregnant women with a history of a previous spontaneous singleton preterm birth, who were at a gestational age between 16 weeks-0 days (16^0) and 20 weeks-6 days (20^6) at randomization. The primary efficacy endpoint was percent of births <37 weeks gestation. Additional endpoints, requested by the FDA, included percent of births <35 weeks and <32 weeks gestation, and a composite index of neonatal morbidity.

The efficacy results of study 17P-CT-002 are summarized in Table 20.

Table 20 Proportion (95% Confidence Interval) of Subjects with Delivery at <37^0, <35^0, <32^0, and <28^0 Weeks Gestational age (FDA Analysis) and Neonatal Morbidity Score

Data Source	17-HPC (N=310)	Vehicle (N=153)	Mean Treatment Differences [A] and 95% Confidence Interval [B]
	%	%	
<37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
<35^0 weeks	21.3	30.7	-9.4% [-18.7%, -0.2%]
<32^0 weeks	11.9	19.6	-7.7% [-16.1.%, -0.3%]
<28^0 weeks	9.4	10.5	-1.1% [-7.4%, 5.2%]
Composite Neonatal Morbidity Score [c]	11.9	17.2	0.1194 (nominal P value)

[A] Chi-square test.

[B] The confidence intervals, based on a t-test, are adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, the final p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

Source: FDA statistical analysis of Applicant's data from Study 17P-CT-002.

c The composite neonatal morbidity measure counted any liveborn infant who experienced death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC. P-values have not been adjusted for multiple comparisons.

Source: Table 11-8, Final Report for Study 17P-CT-002.

The composite index of neonatal morbidity was lower in the 17-HPC group (11.9%, 35/295 infants) than in the vehicle group (17.2%, 26/151 infants) but the between-group difference was not statistically significant.

An Advisory Committee met on August 29, 2006 and made the following efficacy conclusions:

- Prevention of PTB at <35 weeks gestation and especially <32 weeks are better surrogate endpoints for improved infant/childhood outcome.
- Primarily because there are no other available therapies for this major public health problem, the Advisory Committee was supportive of approving this drug with the stipulation that another confirmatory clinical trial be conducted for safety and efficacy.

The major weakness of the original Application in demonstrating efficacy was that it relied for evidence of effectiveness on a single "multicenter" study which did not include a population that was representative of the United States population:

- The percentage of black (African American) subjects in this study was 59%; during the same time frame, the percentage of blacks (African Americans) in the U.S. was 12%. Although the odds ratio of PTB in black couples is 2.4% greater than white couples (Simhan 2008 [2]), and it is prudent to include a disproportionately higher number of blacks (African Americans) in this type of study, this study still does not represent the spectrum of PTB in the U.S..
-

Other limitations of the study included

- It relied on a single multicenter study for evidence of effectiveness.
- There was imbalance in the weighted contribution of the centers. One center (University of Alabama) out of 19 centers in the MFMU Network contributed almost 30% of all subjects.

- The efficacy results of prevention of PTB at < 35 weeks and < 32 weeks (all centers) was not statistically persuasive with the upper bound of the confidence interval approaching 1: -9.4% [-18.7%, -0.2%] reduction in births less than 35 weeks; -7.7% [-16.1.%, -0.3%] reduction in births at less than 32 weeks. There was a disproportionate reduction in PTB < 32 weeks at the University of Alabama center.

The results of some studies in the literature provide *conflicting support for the effectiveness of 17-HPC* for prevention of PTB (Thornton 2007 [3]). Selected publications (see section 6.1.4 for more details) since February 2006 include the following:

- One placebo-controlled study of 17-HPC to prevent PTB in women with twin gestations who had a previous PTB was completed and published by the NICHD Maternal-Fetal Medicine Units (MFMU) Network. *It did not demonstrate effectiveness* (Rouse 2007 [10]); however, further studies are underway to determine if a higher dose is required in multiple gestations..
- Two studies were published based on other sources of progesterone (vaginal progesterone; Prochieve®); efficacy was demonstrated when the at-risk population was defined by *short cervix as a risk factor but not when risk was defined by previous PTB* (Fonseca 2007[8], O'Brien 2007 [9]).

The Applicant (Cytyc) submitted a complete response on April 24, 2008 to the Approvable letter issued by the FDA on October 20, 2006. The proposed confirmatory study is a multi-center, randomized, double-blind, placebo-controlled clinical trial in 1707 women with a singleton pregnancy, aged 16 years or older, with a history of a previous singleton spontaneous preterm delivery. The Division is in agreement with the primary objective of reducing the rate of PTB at < 35 weeks gestation and if statistically significant, the secondary objective of the Neonatal Composite Index would be measured in a hierarchical testing approach.
Pharmacokinetic assessments will be made based on a sparse sampling of approximately 450 subjects (300 active and 150 placebo), stratified according to BMI to analyze the dose-plasma concentration-time relationship of 17-HPC.

Safety Conclusions

Listed below are the overall safety results from study the *NICHD MFMU Network study 17-CT-002:*

- There were *no definitive significant safety issues identified*.
- The FDA is concerned that in the Study 17-CT-002, there was a trend toward an increased risk of miscarriage and stillbirths in the 17-HPC treatment arm, such that, despite a trend toward a decrease in neonatal death, there was no net survival benefit.
- In studies 17P-CT-002 and 17P-IF-001 there was a suggestion that 17-HPC may impair glucose tolerance, requiring further study; also based on trends, there is reason to further study the effects of 17-HPC on amniotic fluid levels and preeclampsia.
- Injection site pain, swelling and pruritus were the most common AEs and reasons for discontinuation in study 17-CT-002.

Since 2006, several publications, with conflicting results, have shed further light on safety of 17-HPC in pregnant women:

Miscarriages/Stillbirths

- One randomized placebo-controlled trial conducted by the NICHD MFMU Network *did not show any specific trend in miscarriage or stillbirth comparing 17-HPC to placebo* (Final study report (b) (4) 2008 [57]).
- One retrospective review of a database revealed a *fetal loss rate at <24 weeks that was comparable to controls, but there was an increased rate of miscarriage in the 17-HPC arm at <20 weeks of gestation* (Gonzalez-Quintero 2007a [11]).

Diabetes in Pregnancy

- In one *retrospective review of a database* 17-HPC had a positive association with an increased incidence of gestational diabetes compared with placebo (Rebarber 2007 [12])

Regarding the *NICHD MFMU Network study 17P-FU:*

- There were *no signals of developmental delay* in the limited follow-up study of children; however, this study was an "ad hoc" addition to the principal study and as such, had some deficiencies, e.g., less than optimum recruitment into the study and lack of neurologic examination in children who screened positive.

In an AERS search by the FDA, six new cases were discovered since October 2006; three were related to preterm labor, therefore not thought to be drug related and no definitive conclusions can be drawn from the single report each of syncope, depression, and congenital heart defect.

In the application submitted by Cytyc, the following safety components are included in the protocol:

- Rule out a doubling of the rate of fetal/early infant death in the 17-HPC group as compared to the placebo group and determine if 17P reduces the rate of stillbirth defined as all stillbirths/fetal deaths/in-utero fetal losses occurring from *20 weeks gestation until term*. The relative risk of fetal/early infant death for the 17-HPC group relative to the placebo group will be determined using the Cochran-Mantel-Haenszel procedure stratified by gestational age at randomization. A two-sided 95% confidence interval (CI) for the relative risk will be constructed using the method of Cochran-Mantel-Haenszel adjusted for gestational age at randomization. If the upper bound of the CI is less than or equal to 2.0, a doubling in the risk of fetal/early infant death can be ruled out.
- Stillbirths/fetal deaths/in-utero fetal losses will have a comprehensive work-up as recommended by the Stillbirth Collaborative Research Network of the National Institute of NICHD, to investigate the cause of death.
- The Applicant proposes to collect and report data on the following complications of pregnancy: gestational diabetes; oligohydramnios; significant antepartum bleeding or hemorrhage; preeclampsia or gestational hypertension; abruption; chorioamnionitis.
- As part of the phase 4 commitments, Cytyc proposes to conduct a follow-up study of children at age 18 to 24 months (when most cases of cerebral palsy and mental retardation can be identified) born to mothers who complete the proposed efficacy and safety trial. The objective of this follow-up study will be to determine whether there are differences in the achievement of developmental milestones between children whose mothers received 17-HPC and those that received placebo.

A full protocol for the follow-up study of children at age 18 to 24 months will be provided for agreement prior to approval.

9.2 Recommendation on Regulatory Action

This reviewer recommends a complete response (approvable) action for Gestiva (17α-hydroxyprogesterone caproate [hereafter referred to as 17-HPC, but also known as HPC and 17P]) for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth. This recommendation is based on one multicenter clinical trial that showed statistically significant reductions in preterm birth (PTB) at <35 and < 32 weeks gestation, both surrogate endpoints acknowledged by an Advisory Committee to predict reduction in neonatal mortality and morbidity. However, the findings from this single study alone are not sufficiently persuasive to support approval alone. Additionally, data from the literature do not consistently demonstrate a decrease in PTB when women with a history of previous PTB are treated with 17-HPC.

During the previous review cycle, the Applicant was asked to provide the Agency with protocols to assess the following efficacy and safety parameters:

- Additional data to provide further statistical support for the effectiveness of 17-HPC to reduce the incidence of PTB at <35 and <32 weeks gestational age.
- Safety studies to assess to potential association of 17-HPC with miscarriages/ stillbirths, and long term developmental and safety evaluations of children at age 18-24 months.

In the Action (Approvable) Letter to the original Applicant (Adeza Biomedical) on October 20, 2006, the Agency indicated a willingness to consider Subpart H approval of 17-HPC for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth, since there is currently no other approved drug in the world for this indication. Approval would be contingent on concurrence with the protocol(s) submitted by the Applicant and the evidence of the feasibility of conducting another randomized, well controlled trial of 17-HPC in women with a history of previous preterm birth (with a follow-up of their children). No studies of 17-HPC for this specific indication have been completed or undertaken in the U.S. since October 2006. This reviewer believes that these critical additional safety and efficacy studies to investigate 17-HPC to prevent PTB in women with a history of previous PTB would not be done in the U.S. without approval under the Subpart H, 21 CFR 314.510.

This reviewer agrees with the overall design of the draft Protocol (hereafter referred to as the "Confirmatory Study") submitted by the Applicant on January 15, 2009, that is designed to:

1. Confirm one of the previous findings of efficacy in Study 17P-CT-002 (i.e., a reduction in preterm births at < 35^0 weeks of gestation),
2. Obtain further information regarding the effect of treatment with 17-HPC on neonatal morbidity and mortality, and
3. Address the concern regarding early pregnancy loss identified in our Approvable letter of October 20, 2006.

In addition, the Applicant has provided a draft protocol for a follow-up study of offspring up to two years of age in the U.S. and in other countries.

In the October 2008 issue of *Obstetrics and Gynecology*, the American College of Obstetrics and Gynecology (ACOG) published COMMITTEE OPINION #419, *Use of Progesterone to Reduce Preterm Birth*[1]. Despite the lack of additional evidence for efficacy of 17-HPC, or any other progesterone, this document states "*Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes."* This sentence is unambiguous, and has been interpreted as an attempt to create a standard of care. A lack of documentation by the health care provider regarding such counsel for women with this risk of PTB can potentially be considered inadequate, or substandard care. This reviewer is concerned that health care providers and Institutional Review Boards, particularly in the U.S., may be reluctant to conduct randomized, placebo controlled trials of 17-HPC for PTB prevention as a result of this recently published ACOG Committee Opinion.

To provide reassurance that these critical studies are conducted, the following is recommended as a condition for possible approval under Subpart H:

- Obtain IRB approval from 15 research centers (both U.S. and non U.S.) to enroll the target number of 1707 subjects. This recommendation takes into consideration that the applicant may need to make changes (add or subtract sites) at a later time.
- Enroll a minimum of 5% of planned subjects (85 subjects [5% of 1707 subjects]); a minimum of 15 subjects should be enrolled from U.S. sites. No site should ultimately enroll more than 15% of all subjects.
- All sites (U.S. and non U.S.) must use the same pre-defined definitions of neonatal morbidity.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management actions are recommended at this time.

9.3.2 Required Phase 4 Commitments

1. The completion of the "Confirmatory Study" described above. This study will need to be initiated prior to approval but will be completed post-approval under Subpart H.

2. The completion of the randomized, double blinded, randomized controlled trial to evaluate developmental and safety issues of the offspring from the Confirmatory Study .

9.3.3 Other Phase 4 Requests

In consultation with the clinical pharmacologist (Dr. Tran), the following phase IV postmarketing commitments were agreed upon (see clinical pharmacology review):

1. The sponsor will provide data characterizing the pharmacokinetics (PK) of 17 α-hydroxyprogesterone caproate (17-HPC) and its metabolites in plasma and urine in pregnant women at several periods throughout the pregnancy.

2. The sponsor will obtain sparse PK samplings as agreed to in the planned Phase 4 efficacy and safety study and analyze the data to assess exposure-response relationships (e.g., time to birth) and effect of body weight and other covariates, as needed, on the PK of 17-HPC.

Approximately 450 subjects from the main clinical trial will participate in the population PK substudy. Subjects in the PK population will be stratified based on BMI (≤ 28 and > 28), such that approximately 40% and 60% of subjects are in each BMI category, respectively.

9.4 Labeling Review

Labeling negotiations were not completed in this review cycle.

9.5 Comments to Applicant

Comments regarding the deficiencies of the current application and the actions needed to resolve these deficiencies should be communicated in the action letter.

10 APPENDICES

10.1 Approvable Letter for NDA 21-945, 20 October 2006

Duplicate Copy

3 Pages Have Been Withheld As A Duplicate Copy Of The Complete Response Letter Dated October 20, 2006 Which Is Located In the "Other Action Letters" Section Of This NDA Approval Package.

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10.2 Efficacy Literature Review

A study comparing 17-HPC with Cerclage to prevent PTB

The use of *17-HPC*, compared with cerclage, for the treatment of short cervix was explored by Rust and colleagues (Rust 2006 Abstract [50]). All patients between 16-24 weeks with a short cervix (2.5cm) and funnel present on transvaginal ultrasound were *randomly assigned* to treatment with transvaginal McDonald cerclage (n=33) or weekly intramuscular injections of 17-HPC (n=31). Otherwise, all patients were treated by an identical protocol. Multiple variables assessing perinatal outcome were analyzed. Maternal demographics, cervical measurements, risk factors for preterm birth, amniocentesis results and urogenital culture results were all similar between groups. The rates of readmission for preterm labor were similar at 56.3% for cerclage vs. 50.0% 17-HPC, p=0.8, as were rates of chorioamnionitis 28.1% vs. 20%, p=0.7; abruption 6.3% vs. 20%, p=0.2; preterm premature rupture of the membranes 28.1% vs. 36.7%, p=0.7 and perinatal death 15.6% v 10.0%, p=0.7. *The mean gestational age at delivery was 32.4 wk for cerclage vs. 32.9 wk for 17-HPC, p=0.4.*

Medical Officer's Comments:

- *This study suggests that 17-HPC may act on the cervix to prevent PTB; however, the study was underpowered to demonstrate significant statistical differences*

Two studies published based on other sources of progesterone (vaginal progesterone;

Prochieve®); efficacy was demonstrated when the at-risk population was defined by short cervix as a risk factor but not when risk was defined by previous PTB:

The use of vaginal progesterone to reduce spontaneous delivery before 34 weeks was evaluated in women with a cervical length of 15 mm or less in a randomized, double-blind placebo-controlled trial by Fonseca and colleagues (Fonseca 2007 [8]). Cervical length was measured by trans-vaginal ultrasonography from 20 to 25 weeks gestation in 24,620 women. Cervical length was ≤ 15 mm in 413 of the women (1.7%) and 260 of these 413 women were randomized to receive vaginal progesterone (200 mg each night) or placebo from 24 to 34 weeks gestation. Spontaneous delivery before 34 weeks gestation was less frequent in the progesterone group than in the placebo group (19.2% vs. 34.4%; relative risk, 0.56; 95% CI, 0.36 to 0.86). Progesterone was associated with a nonsignificant reduction in neonatal morbidity.

Medical Officer's Comment:

- *The results of this study suggest effectiveness of vaginal (natural) progesterone to prevent PTB in women whose risk factor is a short cervix.*
- *The data also suggest prevention or slowing of cervical shortening may be one of the mechanisms by which progesterone reduces preterm birth.*

O'Brien and colleagues reported results from a randomized, placebo-controlled study (ProVagGel Study) that investigated the efficacy and safety of progesterone vaginal gel (90 mg daily of intravaginal progesterone - Prochieve®) for the reduction of recurrent preterm birth (O'Brien 2007a[9]). The study randomized 659 pregnant women with a history of spontaneous preterm birth who started study treatment between 18^0 and 22^6 weeks gestation (309 progesterone; 302 placebo). *The primary outcome was preterm birth at ≤32 weeks gestation, which was not different between the progesterone and placebo groups (10.0% vs. 11.3%).* From the same ProVagGel Study, O'Brien and colleagues reported on a secondary analysis of data collected (O'Brien 2007b [9]). The analysis explored whether daily intravaginal progesterone gel altered the rate of cervical shortening in women at increased risk for preterm birth. Transvaginal cervical length measures were obtained at randomization (18-22^6 weeks) and at 28 weeks gestation. Data were available for 611 subjects (309 progesterone; 302 placebo). Initial mean baseline cervical length was 3.7 cm for both groups. At the 28 week exam, the progesterone group had a significantly longer cervix than the placebo group (3.3 cm progesterone vs. 3.1 cm placebo ($p<0.001$).

Medical Officer's Comments:

- *This is the largest published randomized controlled trial of any type of progesterone to date. It did not did not show efficacy at preventing PTB at ≤ 32 weeks, or <37 weeks.*
- *These observations from secondary analyses suggest that the association between cervical length and response to progesterone (including 17-HPC) may be worth exploring in randomized controlled trials.*

A placebo-controlled study of 17-HPC to prevent PTB in twin gestations

A multicenter, randomized, double-blind, placebo-controlled NICHD-sponsored study (MFMU Network) investigated the use of 17-HPC (250 mg IM weekly) for the prevention of preterm birth (<35 weeks) in twin gestations (Rouse 2007a[10]). Women carrying twins with a gestational age of 16 - 20[3] weeks were eligible for randomization. A total of 655 women were analyzed: 325 received 17-HPC and 330 received placebo. In this study, 17-HPC did not reduce preterm birth: delivery or fetal death before 35 weeks of gestation occurred in 41.5% of pregnancies in the 17-HPC group and 37.3% in the placebo group (relative risk [RR]: 1.1; 95% CI: 0.9, 1.3).

Medical Officer's Comments:

- *In summary, this study does not support the use of 17-HPC to reduce the risk of preterm birth in twin gestations. Relevant to the indication of prevention of recurrent preterm birth, fewer than 10% of women in this study had previously given birth prematurely.*
- *The dose of 17-HPC (250 mg per week), which has shown some benefit in singleton pregnancies, may need to be increased because plasma volume is known to be approximately 20% greater in twin compared to singleton gestations.*
- *It is important to note that there was not a significant difference in the rate of fetal deaths between the treatment arm and placebo arm (see section 7.2.3 for a more detailed discussion).*

Two randomized controlled trials published that suggested that 17-HPC's effect may not be related to the gestational age or occurrence of contractions prior to treatment.

17-HPC Use after Onset of Labor

Facchinetti and colleagues evaluated whether 17-HPC treatment affects cervical length after an incident of preterm labor (Facchinetti 2007 [51]). Hospitalized patients remaining undelivered after a preterm labor episode occurring at 25-33 weeks, were *randomly allocated* either to observation (n=30) or to receive ***341 mg*** *of intramuscular 17-HPC* (n=30) every 4 days until gestational week 36. A transvaginal ultrasound measure of cervical length was performed at discharge and days 7 and 21 after discharge. The observation group reported a progressive shortening of the cervical length that was significantly greater than the 17-HPC group both at day 7 (2.37 vs. 0.83 mm; p=0.002) and day 21 (4.60 vs. 2.40 mm; p=0.002). Treatment with 17-HPC was associated with both a reduction in the risk of cervical shortening of 4 mm (odds ratio [OR]: 0.18; 95% CI: 0.04, 0.66) and in the risk of preterm delivery (OR: 0.15; 95% CI: 0.04, 0.58). *The incidence of preterm delivery <37 weeks was 57% in the observation group compared to 16% in the 17-HPC group (p=0.004).* The incidence at <35 weeks was 23.3% compared to 10%, respectively. Based on this small patient population, the authors conclude that *high-dose 17-HPC* reduces preterm delivery after an incident of preterm labor in patients at risk because of *shortened cervix*.

Medical Officer's Comment:

- *These results appear to suggest effectiveness of a higher dose of 17-HPC to prevent recurrent PTB and stress the need for dose-finding studies and refinement of defining the "at risk" population.*

Two retrospective studies evaluating the effect of gestational age at 17-HPC initiation showed similar but slightly different results:

How and colleagues explored the effectiveness of 17-HPC prophylaxis by gestational age at 17-HPC initiation (How 2007 [52]). This retrospective analysis was based on data from a Matria Healthcare database of women with singleton pregnancy and prior preterm birth who received outpatient 17-HPC prophylaxis for prevention of spontaneous preterm delivery. Data were stratified by gestational age at 17-HPC initiation: 1) 16-20.9 weeks (n=599), and 2) 21-26.9 weeks (n=307). These groups were further stratified according to the number of prior preterm deliveries (1, 2, or >2). Neonatal mortality was infrequent in both groups. There were 3 stillbirths (0.5%) and 3 neonatal deaths in the early initiation group (Group 1) and 2 stillbirths and 1 neonatal death in the late initiation group (Group 2). No significant differences were found in the gestational age at delivery or in rates of recurrent preterm birth at <37, <35, and <32 weeks between women initiating 17-HPC at 16-20.9 weeks or 21-26.9 weeks overall or when stratified by number of prior preterm births. *The authors concluded that "initiation of 17-HPC prophylaxis between 21 and 26.9 weeks gestation was as effective as initiation between 16 and 20.9 weeks. These data show that the later initiation of 17-HPC still imparts benefit for women with 2 and >2 prior preterm births who are at especially high risk for recurrent preterm births".*

Medical Officer's Comment:

- *These findings are interesting since other unpublished secondary analyses suggest otherwise. This was a retrospective study that did not have specific data on baseline cervical length, gestational age of prior preterm birth, maternal race, or complete neonatal outcomes. A well-controlled study is needed to confirm the authors' conclusion.*

Gonzalez-Quintero and colleagues (Gonzalez-Quintero 2007b[11]) did an earlier exploration of the Matria Healthcare database on the question of gestational age at initiation of 17-HPC, and most probably is based on a *patient population that either overlaps significantly or is totally contained in the dataset analyzed and published* in September 2007 by How and colleagues (How 2007 [52]). The sample size in the report by Gonzalez-Quintero and colleagues [11] was 156 women who initiated 17-HPC at 16-20 weeks' gestation and 119 women who initiated 17-HPC at 21-26 weeks' gestation. Inclusion criteria were patients enrolled in an outpatient preterm birth prevention program from April 2004 to April 2005, who had a singleton pregnancy and a history of prior preterm delivery and were without symptoms of preterm labor at time of enrollment. *Gestational age at delivery was similar for each group, as was the rate of preterm delivery at <35 and <32 weeks. However, a numerically greater percentage of women with later initiation of 17-HPC delivered at <37 weeks due to spontaneous preterm labor than those with earlier initiation of 17-HPC (37.0% vs. 26.3%; p=0.065).*

Medical Officer's Comment:

- *Interestingly, these findings trend in the opposite direction to those of How and colleagues.*
- *It is again worth noting is that this was a retrospective data analysis, not a randomized, controlled study.*

Additional *in-vitro* data have been published, which will eventually elucidate mechanisms, kinetics etc.:

Many *in vitro* studies have been reported in abstracts submitted to either the 2007 or 2008 annual SMFM meetings. These *in vitro* studies explored: 1) the mechanism of action of 17-HPC for the prevention of preterm birth; 2) how 17-HPC is metabolized; and 3) distribution of 17-HPC across the placenta. The following studies were selected for this review:

Paonessa and colleagues explored how 17-HPC prevents preterm birth using an *ex vivo* placental cotyledon model, which was designed to determine if 17-HPC has a vasoactive effect on fetoplacental vasculature (Paonessa 2006 [64]). Five placentas from normal parturients were obtained within 15 minutes of delivery at 37 to 42 weeks' gestation. Two cotyledons were obtained from each of 5 placentas. One cotyledon from each pair was infused with a perfusate containing U46619, a thromboxane sympathomimetic. After 30 minutes, a dose of 17-HPC (0.5 mL of 200 nmol/L) was administered to each cotyledon. Finally, a vasoconstricting dose of angiotensin II was injected into the circulation of each cotyledon to verify vascocontractile potential in both cotyledons and fetoplacental vascular pressure response was recorded. Infusion with U46619 significantly increased the perfusion pressure in the cotyledons (60.1 mm Hg vs. 29.5 mm Hg; p=0.008). The addition of 17-HPC significantly lowered the perfusion pressure in the U46619-infused cotyledons for the 30 minutes post-administration compared with the 30 minutes pre-administration (60.1 mm Hg vs. 27.3 mm Hg; p=0.03), but had no effect on the perfusion pressures in the cotyledons that were not pre-constricted with U46619 (30.6 mm Hg vs. 30.1 mm Hg; p=0.48). Both groups of cotyledons responded with vasoconstriction to angiotensin II with no difference in response between groups.

Medical Officer's Comments:

- *This study confirmed that the vasorelaxant effects of 17-HPC seen in prior animal models are also manifest in the fetoplacental vasculature of human placental cotyledons.*
- *The vasorelaxant effect may be another mechanism by which 17-HPC prevents preterm delivery and may provide additional therapeutic fetal benefits beyond the prevention of preterm labor.*

Mechanism of Action Studies

- Progestational agents (Pas) significantly modulate gene expression in the cervix in the presence and absence of inflammation. The regulation of these pathways, specifically claudin proteins, may be a *critical mechanism by which PAs prevent preterm birth*, especially in women with premature cervical shortening (Xu 2008 [65])
- A competitive steroid hormone receptor binding assay, using cytosols expressing either recombinant human progesterone receptor-A or -B, or rabbit uterine or thymic cytosols, was used to assess the binding affinity of 17-HPC. *Binding to progesterone receptors, glucocorticoid receptors, or expression of progesterone-response genes is no greater with 17-HPC than with progesterone. The authors suggest that another mechanism must account for the beneficial effect* of 17-HPC (Attardi 2007 [66]).
- Fetal membranes, collected from women undergoing elective cesarean delivery or delivering after spontaneous labor, were tested for the extent and localization of nuclear progesterone

receptor (nPR) expression in amnion, chorion, and deciduas. In this study nPR expression was limited to the deciduas and the *data suggest that progesterone maintains pregnancy in part by affecting decidual cell function* and not by its direct actions on the amnion or chorion (Merlino 2007 [67]).

- Myometrial tissues obtained from the lower uterine segment of women at term undergoing cesarean section were used to determine whether progesterone or 17-HPC directly inhibits human uterine contractility in vitro. In this model, *natural progesterone suppressed myometrial contractility*, while the effects of 17-HPC were difficult to assess, because a large proportion of the tissue samples was lost during incubation, but, surprisingly, *17-HPC* was reported to *stimulate* contractions (Ruddock 2007 [68]).
- *Salivary Estrogen Levels:* Klebanoff and colleagues reported in an abstract on the effect of 17-HPC, compared with placebo, on salivary progesterone (PROG) and estriol (E3) concentrations in gravidas at risk for recurrent preterm birth (Klebanoff 2008 [69]). Weekly salivary samples from 40 women who received 17-HPC and 40 who received placebo in the NICHD study (17P-CT-002) were analyzed for PROG and E3 levels and E3:PROG ratios. Longitudinal modeling, accounting for repeated measures, found the trajectory of PROG with advancing gestation did not differ between 17-HPC and placebo-treated women. However, the rate of rise in salivary E3 was greater in the placebo than the 17-HPC-treated women (p-values 0.01 for weeks 1-4 and 0.23 for weeks 1-8 of treatment). The E3:PROG ratio increased during pregnancy in the placebo group, but remained flat in the 17-HPC group (p-values for difference in trajectories 0.10 for weeks 1-4 and 0.003 for weeks 1-8). *Compared with placebo, 17-HPC slows the rise in salivary E3 and especially in the E3:PROG ratio. This finding could explain the reduction in preterm birth with 17-HPC treatment.*

Medical Officer's Comment:

- *Multiple investigators have conducted, and are continuing to conduct investigations to aid in the mechanistic understanding of the effectiveness of 17-HPC (and other progesterones) to prevent PTB.*

10.3 Line-by-Line Labeling Review

Detailed review of the label will be deferred until the next review cycle.

10.4 References

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/s/

Barbara D. Wesley
1/23/2009 02:37:19 PM
MEDICAL OFFICER

Lisa Soule
1/23/2009 02:48:22 PM
MEDICAL OFFICER
I concur with Dr. Wesley's recommendation that the Gestiva Complete Response submission receive a Complete Response (Approvable) action.

Cross-Discipline Team Leader Review

Date	January 22, 2009
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	21-945 Complete Response submission
Applicant	Cytyc Corporation
Date of Submission	April 25, 2008
PDUFA Goal Date	October 24, 2008
PDUFA Goal Extension Date	January 23, 2009
Proprietary Name / Established (USAN) names	Gestiva Hydroxyprogesterone caproate
Dosage forms / Strength	Intramuscular injection; 250 mg/ml once weekly
Proposed Indication(s)	Prevention of preterm birth in women with a history of at least one spontaneous preterm birth
Recommended:	***Complete Response (Approvable)***

1. Introduction

Preterm birth, defined as delivery prior to 37 completed weeks of gestation, is a significant public health problem in the United States with increasing prevalence, currently affecting 12% of all births. Although there are a number of diagnostic tests proposed to identify women at risk for preterm labor and medications used off-label to treat preterm labor, there are no data indicating a benefit on neonatal morbidity or mortality from any of these interventions.

In 1998, the National Institute of Child Health and Human Development (NICHD) initiated a multicenter, double blind, 2:1 randomized, vehicle-controlled clinical trial through its Maternal-Fetal Medicine Units (MFMU) Network to evaluate the safety and efficacy of hydroxyprogesterone caproate (also known as 17-α-hydroxyprogesterone caproate or 17-HPC) in pregnant women with a history of spontaneous preterm birth. The initial trial (hereinafter referred to as 17P-IF-001) was terminated after about one year when the study drug was recalled by its manufacturer at the request of the FDA, due to violations of manufacturing processes that potentially could affect drug potency. At termination, only 150 of 500 planned women had been randomized, and only 86 women (57 of 17-HPC-treated women and 29 of vehicle-treated women) had completed treatment.

The trial (referred to as 17P-CT-002) was started anew and enrolled 463 of a planned 500 women before being terminated prematurely due to crossing the prespecified threshold for efficacy as determined by the Data Safety Monitoring Board. Results of the trial were published in the New England Journal of Medicine in June 2003[1]. The American College of Obstetrics and Gynecology (ACOG) issued a Committee Opinion[2] in November 2003 stating

[1] Meis PJ et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 348: 2379-85, 2003.

[2] ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 291, November 2003

that "further studies are needed to evaluate the use of progesterone in patients with other high-risk obstetric factors, such as multiple gestations, short cervical length, or positive test results for cervicovaginal fetal fibronectin. When progesterone is used, it is important to restrict its use to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug." However, this opinion was viewed as supportive of the use of 17-HPC for prevention of recurrent preterm birth, and use of compounded 17-HPC has increased substantially since 2003.

2. Background

2.1 DESCRIPTION OF PRODUCT

The drug substance (17-HPC) was approved in 1956 under NDA 10-347 (with additional indications approved in 1972 under NDA 16-911) and marketed under the trade name Delalutin® for a variety of gynecological indications as well as for prevention of habitual, recurrent and threatened miscarriage. The Delalutin sponsor discontinued marketing in the 1990's, and the NDAs were withdrawn "without prejudice" by the Agency in 2000. However, particularly since the publication of the 2003 New England Journal of Medicine article, 17-HPC has been compounded by pharmacists and used in women at risk of preterm birth.

Team Leader Comment:

- ***Delalutin® was not withdrawn from the market due to safety concerns, nor were efficacy concerns noted at the time of withdrawal.***

The proposed dosing regimen is a weekly 1 mL intramuscular injection of 250 mg of 17-HPC in castor oil with 46% benzyl benzoate and 2% benzyl alcohol, beginning at 16 weeks 0 days (16^0) to 20 weeks 6 days (20^6 weeks) gestation and used through 36^6 weeks gestation or birth.

2.2 REGULATORY HISTORY

2.2.1 Background and Material Reviewed in First Cycle Review

The original Applicant, Adeza Biomedical, submitted a preIND (68,108) and met with the Division of Reproductive and Urologic Products (hereinafter referred to as DRUP or the Division) on January 30, April 5 and July 16, 2004 to discuss the submission of a 505(b)(2) application based upon the NICHD trial. Issues of concern that were conveyed to Adeza in these discussions included:

- The Division did not agree that adequate replicate evidence of the safety and effectiveness of 17-HPC for the prevention of recurrent preterm birth existed in the literature.
- Usually, either two adequate and well-controlled studies or a single study with a robust and compelling outcome and strong supporting data would be required to support approval of a new drug product. Data from the NICHD trial might not suffice to demonstrate the safety and effectiveness of 17-HPC.
- The utility of the published study's primary endpoint, reduction of preterm birth at <37 weeks of gestation; the Division believed that delivery at <32 weeks was more clinically important, as the majority of neonatal morbidity and mortality occurs in infants born at <32 weeks. In addition, the Division would focus on reduction of

morbidity and mortality, rather than on increasing the gestational age at delivery without any associated clinical benefit.

- Absence of follow-up data of children exposed *in utero* to 17-HPC was noted; follow-up of at least 35-50% of exposed babies in each treatment arm through at least two years of age was requested.
- Data from Study 17P-IF-001 should also be submitted in the NDA, as should all literature addressing the use of 17-HPC for prevention of recurrent preterm birth.

A preNDA meeting was held on June 27, 2005, and the original application was submitted on April 20, 2006. The initial NDA submission provided pivotal safety and efficacy data from a single multicenter controlled trial (NICHD Study 17P-CT-002) to support the safety and efficacy of 17-HPC for the prevention of recurrent preterm birth. In addition, the Applicant submitted the data from the terminated initial efficacy study 17P-IF-001, and data from a follow-up study of infants delivered to mothers enrolled in 17P-CT-002 (this study is referred to as 17P-FU), which was conducted at the Division's request. Details of these three studies are synopsized in Table 1.

Table 1 Clinical Studies of 17-HPC in NDA 21-945

Protocol # /Status	Study Design	Study Population	Treatment Dose	Duration of Drug Treatment	Number of Subjects Enrolled	Number of Black/Non-Black Subjects	Mean Age (Range)
17P-IF-001 Terminated Mar 1999[A]	Double-blind, Placebo-controlled, Randomized 2:1 active treatment to Placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 37^0 wks gestation or delivery	Total: 150 17P: 94 Placebo: 56	Total: 95/55 17P: 54/40 Placebo: 41/15	26.2 yr (17, 42)
17P-CT-002 Completed Aug 2002[B]	Double-blind, Placebo-controlled, Randomized 2:1 active treatment to Placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 37^0 wks gestation or delivery	Total: 463 17P: 310 Placebo: 153	Total: 273/190 17P: 183/127 Placebo: 90/63	26.2 yr (16, 43)
17P-FU Completed Nov 2005	Observational long-term safety follow-up for Study 17P-CT-002	Infants discharged live in Study 17P-CT-002	None	No study treatment was administered	Total: 278 17P: 194 Placebo: 84	Total: 152/126 17P: 105/89 Placebo: 47/37	47.4 mo (30, 64)

[A] Study 17P-IF-001 was terminated early by the Sponsor when the manufacturer recalled the study drug. The last subject visit was in August 1999. Of the 150 subjects, 104 subjects (65 randomized to 17-HPC and 39 randomized to vehicle) had ended their treatment prior to the study termination either because they had completed treatment with study drugs (i.e., completed study treatment to 36^6 weeks of gestation or delivery) or had withdrawn prematurely for reasons other than recall of study drugs.

[B] An independent Data and Safety Monitoring Committee (DSMC) reviewed the study data after 400 subjects had completed the study. Based on that interim dataset, the primary endpoint, birth $<37^0$ weeks of gestation in the 17-HPC group, was significantly reduced and the p-value was below the p-value specified in predefined stopping rules. The DSMC recommended that enrollment in the study be stopped, so that no new subjects would be assigned placebo. By the time the study was stopped, 463 subjects had been enrolled, which was 92.5% of the proposed sample size of 500 subjects.

Source: Prepared by Medical Reviewer from final Study Reports.

2.2.2 Efficacy Results in First Cycle Review

Details on the demographics of the population enrolled in Study 17P-CT-002 are in the reviews of the original 2006 NDA. While there were no significant differences between treatment arms in the distribution of demographic and baseline characteristics, it is notable that almost 60% of subjects in both the 17-HPC and placebo arms were African-American. Distribution of the sample over the 19 participating MFMU Network centers was also of concern; some sites enrolled as few as two subjects, while the University of Alabama enrolled 27% of the total.

Team Leader Comments:

- ***Generalizability of the study results may be limited by the enrollment of African-American subjects at a rate far exceeding their distribution in the general population.***

- ***Heavy reliance on a single site for a large fraction of the study population is in contrast to stated characteristics[3] of a single study that could provide adequate support for an efficacy claim.***

The primary efficacy endpoint in Study 17P-CT-002 was percent births at <37 weeks gestation. Additional endpoints requested by the FDA included percent births at <35 weeks and at <32 weeks gestation, and a composite index of neonatal mortality and morbidity. The composite index was based on the number of infants who experienced any one of the following: death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis or necrotizing enterocolitis (NEC).

The primary efficacy endpoint was analyzed using the intent to treat (ITT) population. Outcome data were available on all women (except the four in the 17-HPC group who were lost to follow-up) even if they withdrew from treatment prior to delivery. Results for this and secondary endpoints, as calculated by the FDA Statistical Reviewer, are displayed in Table 2. The results at <37 weeks continued to favor 17-HPC when subgroup analyses categorized by gestational age of qualifying preterm birth, maternal race and number of previous preterm births were conducted.

Table 2 Efficacy Results – Study 17P-CT-002

Gestational Age [a]	17-HPC[a] (N=310)	Vehicle (N=153)	Treatment difference [95% Confidence Interval, adjusted for interim analyses [b]]
	%	%	
$<37^0$ weeks	37.1	54.9	-17.8%[-28%, -7%]
$<35^0$ weeks	21.3	30.7	-9.4%[-18.7%, -0.2%]
$<32^0$ weeks	11.9	19.6	-7.7%[-16.1.%, -0.3%]
$<28^0$ weeks	9.4	10.5	-1.1%[-7.4%, 5.2%]

[a] Four 17-HPC-treated patients were losses-to-follow-up. They are counted as deliveries at their gestational ages at time of last contact (18.6, 22.0, 34.4 and 36.6 weeks, respectively).
[b] To preserve the overall Type I error rate of 0.05, the adjusted confidence intervals (equivalent to a 96.6% confidence interval) use the final p-value boundary of 0.0345.

Source: FDA Statistical Review (First Cycle), Table 3.1, page 14, dated October 19, 2006

Team Leader Comments:

- ***There was a statistically significant treatment effect of 17-HPC in preventing recurrent preterm birth at <37, <35 and <32 weeks, which remained consistent over varying levels of risk, as measured by maternal race, number of prior preterm births and gestational age of qualifying preterm birth.***
- ***However, the rate of preterm birth at <37 weeks in the placebo group was higher than that typically reported in trials in a similar population (e.g., other trials within the MFMU Network). The rate in the 17-HPC group was more consistent with that typically seen in an untreated population.***

The Applicant also provided an assessment of the proportion of infants in each treatment arm with one or more events making up the composite index endpoint of neonatal morbidity/mortality. Although there was a lower proportion of subjects in the 17-HPC group (11.9% vs. 17.2% in the vehicle group) who experienced at least one event of the composite endpoint, this difference was not statistically significant.

[3] Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998

Team Leader Comment:

- ***The clinical trial was not powered to show a reduction in infant morbidity/mortality.***

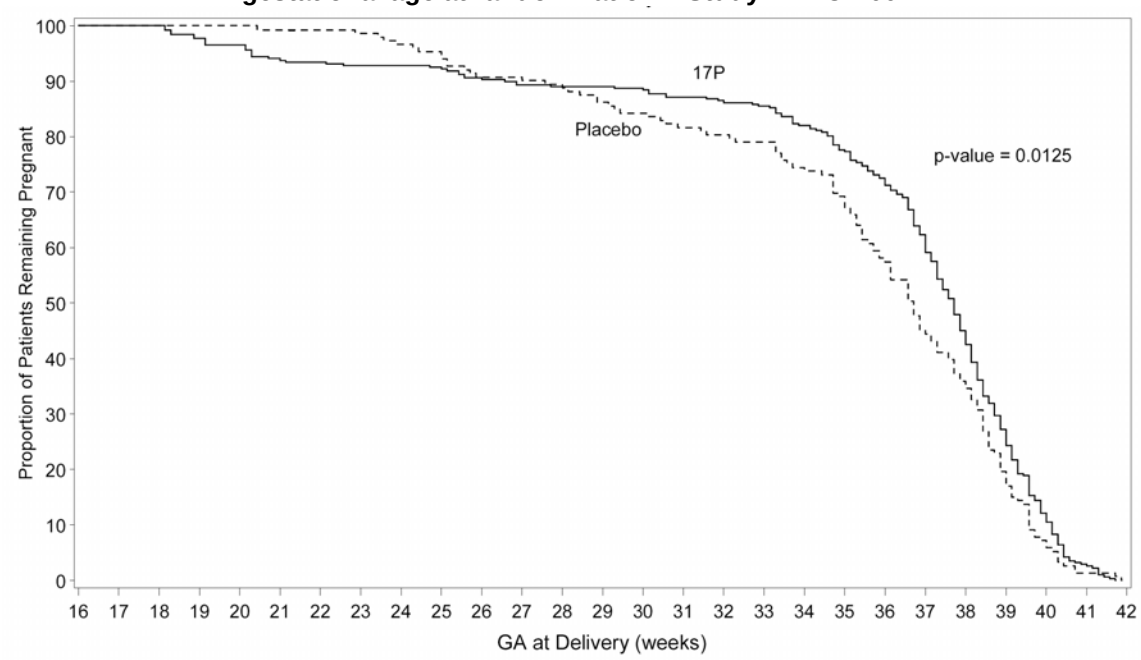
Individual components of the mortality/morbidity composite endpoint were also assessed, as were other outcome measures such as use of supplemental oxygen. Of 15 measures of neonatal morbidity evaluated, three were statistically significantly different, favoring a treatment effect for 17-HPC: use of supplemental oxygen (15% vs. 24%), any IVH (1.4% vs. 5.3%) and NEC (0 vs. 2.7%). There was also a numerical decrease in the neonatal mortality rate (2.6% in the 17-HPC arm vs. 5.9% in the placebo arm), but this was not statistically significant.

Team Leader Comment:

- ***The analyses of individual neonatal morbidity endpoints were not adjusted for multiple comparisons and may not represent true treatment effects.***

Pregnancy subsequent to the time of randomization was maintained for an average of six days longer in the 17-HPC group (131 vs. 125 days), with the mean gestational age at delivery being one week greater (36.2 vs. 35.2 weeks for 17-HPC and vehicle subjects, respectively). The Applicant provided a Kaplan-Meier analysis of the time to delivery in the two arms of the study, which showed a statistically significant difference in the shape of the curves by the log-rank test (see Figure 1).

Figure 1 Time to delivery as a function of gestational age, using staggered entry based on the gestational age at randomization – Study 17P-CT-002



Source: Applicant Response to FDA's request dated 7/20/06

Team Leader Comment:

- ***The Kaplan-Meier curve demonstrates the prolongation of time to delivery in the 17-HPC group starting at about 28 weeks. Prior to about 26 weeks, however, the 17-HPC group has a higher rate of preterm delivery, attributable primarily to miscarriages and second trimester stillbirths (see Section 2.2.3).***

Upon determination that the University of Alabama had contributed 27% of the sample size of Study 17P-CT-002, the Division requested that the Applicant provide a table analyzing the primary and key secondary endpoints for that single site, for all other sites and for all centers. Results are presented in Table 3.

Table 3 Percentages of Preterm Births at <37, <35, and <32 Weeks Gestation – Effect of Largest Center – Study 17P-CT-002

Gestation (weeks)	Percentage of Preterm Births								
	University of Alabama			All Other Centers Combined			All Centers		
	17-HPC (n=86)	Vehicle (n=40)	**Diff.**	17-HPC (n=224)	Vehicle (n=113)	**Diff.**	17-HPC (n=310)	Vehicle (n=153)	**Diff.**
<37	26.7	45.0	**-18.3**	41.1	58.4	**-17.3**	37.1	54.9	**-17.8**
<35	17.4	27.5	**-10.1**	22.8	31.9	**-9.1**	21.3	30.7	**-9.4**
<32	10.5	25.0	**-14.5**	12.5	17.7	**-5.2**	11.9	19.6	**-7.7**

Source: Applicant's submission of October 10, 2006

Team Leader Comment:

- ***Although the rates of preterm birth at <37 and <35 weeks were lower in both arms of the University of Alabama sample than in all other centers, the treatment effect (i.e., the difference in preterm delivery rate between 17-HPC and vehicle arms was comparable for the Alabama site and the other centers combined, suggesting a stable treatment effect across centers. However, the rates of preterm birth at <32 weeks diverged from the overall study trend at the University of Alabama site – the preterm birth rate was higher in the vehicle arm and lower in the 17-HPC arm than in all other centers combined, leading to a much higher treatment difference at <32 weeks at the Alabama site than in all other centers and in the study as a whole.***

The Applicant conducted several analyses to assess the possibility of a center effect, including an efficacy analysis with and without the University of Alabama site, a center-by-treatment interaction analysis using logistic regression, evaluation of consistency of treatment effect across centers using the Breslow-Day statistic and an analysis adjusted for center using the Cochrane-Mantel-Haenszel statistic. The Applicant noted that the treatment differences at <32 weeks with (-7.7) and without (-5.2) the University of Alabama data were similar, as were the relative risks of birth <32 weeks (0.68 with and 0.70 without the University of Alabama data). The remaining analyses were also interpreted by the Applicant to show little likelihood that the effect at <32 weeks was being "driven" by this single center.

Team Leader Comments:

- ***Although the Applicant's analyses appear satisfactory, the large contribution to the total sample size by a single site for the <32 week outcome was of concern in an application that relied upon a single clinical trial to demonstrate efficacy.***
- ***There were also exploratory analyses by the FDA Statistical Reviewer that suggested there might be an effect of the time of treatment initiation on efficacy: here again, disproportionate enrollment of women early in the eligibility window for gestational age at the University of Alabama might have impacted these results. These concerns further supported the decision that a confirmatory trial would be needed to evaluate whether the efficacy results can be replicated in different centers.***

Although questions about the potency of the study drug used in Study 17P-IF-001 limit the reliability of its findings, the data were reviewed for efficacy and safety. There was no

evidence of a treatment effect on the proportion of deliveries at <37 weeks (41.5% in the 17-HPC arm as compared to 35.7% in the placebo arm).

2.2.3 Safety Results in First Cycle Review

Subject disposition was comparable over the two study arms of Study 17P-002, with approximately 90% of each treatment group completing the study. Four subjects, all in the 17-HPC arm, were lost to follow-up. Of those withdrawing prematurely from the study, the percent due to an adverse event (AE) was 22% in the 17-HPC arm and 21% in the placebo arm.

There were no maternal deaths in either Study 17P-IF-001 or Study 17P-CT-002. Serious unexpected non-fatal adverse events occurred in three women and one infant exposed to 17-HPC. These included a postpartum pulmonary embolus, cellulitis at the injection site after the 8th injection, postpartum hemorrhage and respiratory distress after a 21 week stillbirth, and a male infant delivered at 37^5 weeks with infarcted testicles secondary to intrauterine torsion.

The numbers of miscarriages, stillbirths, and neonatal deaths in each of the treatment groups are listed in Table 4. Five of 306 subjects assigned to the 17-HPC group experienced miscarriages. No subject in the vehicle group miscarried. The incidence of stillbirths was slightly higher in the 17-HPC group, but the difference was not statistically significant. Overall eight subjects had stillbirths: six (2.0%) subjects in the 17-HPC group and two (1.3%) subjects in the vehicle group. The incidence of neonatal deaths was numerically twice as high in the vehicle group (6.0% vs. 2.7%, but the difference was not statistically significant. The overall incidence of fetal and neonatal mortality was similar in the two treatment groups ([6.2% in the 17-HPC group and 7.2% in the vehicle group).

Table 4 Miscarriages, Stillbirths, and Neonatal Deaths - Study 17P-CT-002

Pregnancy Outcome	17-HPC N=306 n (%) [A]	Vehicle N=153 n (%) [A]	Nominal P-value [B]
Miscarriages <20 weeks gestation	5 (2.4)[C]	0	0.17
Stillbirth	6 (2.0)	2 (1.3)	0.72
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.12
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.69**

[A] Percentages are based on number of enrolled subjects and not adjusted for time on drug.
[B] No adjustment for multiple comparisons
[C] Percentage adjusted for the number of at risk subjects (n=211) enrolled at <20 weeks gestation.
Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

Team Leader Comments:

- ***A similar 17-HPC-associated increase in miscarriages and stillbirths was not observed in Study 17P-IF-001.***
- ***However, a meta-analysis of four published studies[4] also showed a possible association of 17-HPC with miscarriage, demonstrating a nonsignificant odds ratio of 1.30 (95% confidence interval 0.61 to 2.74).***

[4] Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Brit J Obstet Gynecol 97: 149-54, 1990

- ***The similar gestational ages at delivery of the infants who died in the neonatal period suggests that there would be little difference in the gestational age-adjusted neonatal death rate between the groups. It appears that the decreased neonatal death rate in the 17-HPC arm is attributable to a lower proportion of early preterm deliveries as compared to the vehicle arm.***
- ***There was no difference in the overall fetal/neonatal death rate between the two arms; the reduction in neonatal death in the 17-OHPC group was offset by the increased rate of fetal loss. Thus, there was no net survival benefit to offspring of women treated with 17-HPC in Study 17P-CT-002.***

Congenital anomalies were noted in 2% of each treatment group in Study 17P-CT-002, with a similar range of defects, including genitourinary and cardiovascular anomalies.

Team Leader Comment:

- ***The general population background rate for congenital anomalies is 2-3%.***

Discontinuation due to adverse events occurred in seven 17-HPC subjects and four vehicle subjects. Urticaria and injection site pain were the most common reasons for discontinuation. The most common adverse events in the 17-HPC and vehicle groups, respectively, were injection site pain (35% and 33%), injection site swelling (17% and 8%), pruritis, including injection site pruritis (14% and 9%), urticaria (12% and 11%), nausea (6% and 5%), contusion (6% and 9%), and neonatal death (6% and 3%).

Maternal complications were reported in both Studies 17P-CT-002 and 17P-IF-001. The proportion of women with three relatively common pregnancy complications (gestational diabetes, oligohydramnios and preeclampsia) was nonsignificantly higher in both studies in the 17-HPC arm as compared to the vehicle arm (see Table 5).

Table 5 Selected Pregnancy Complications: Studies 17P-CT-002 and 17P-IF-001

Pregnancy Complication	Study	17-HPC N (%)	Vehicle N (%)
Gestational Diabetes	CT- 002	17 (5.6)	7 (4.6)
	IF- 001	8 (8.6)	0 (0.0)
Oligohydramnios	CT- 002	11 (3.6)	2 (1.3)
	IF- 001	2 (2.2)	1 (1.9)
Preeclampsia	CT- 002	27 (8.8)	7 (4.6)
	IF- 001	6 (6.5)	2 (3.8)

Source: Primary Medical Review (First Cycle), p 57, dated October 19, 2006, adapted from table 12-3 Final Report for Study 17-CT-002

Team Leader Comment:

- ***All three of these complications are identified more frequently as pregnancy advances; therefore the apparent increased rates may be attributable to the prolongation of pregnancy in the 17-HPC arm, rather than to an adverse effect of the drug.***

At the FDA's request, the Applicant conducted an infant/toddler follow-up study (Study 17P-FU) to provide outcome data at two years of age or greater on the children born to women treated in Study 17P-CT-002 (194 subjects exposed *in utero* to 17-HPC and 84 exposed to vehicle were enrolled). Details are provided in the clinical reviews of the 2006 submission.

The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received 17-HPC compared with placebo during the pregnancy in Study 17P-CT-002.

There were no deaths in either group following discharge from the birth hospitalization. There were no differences between the two arms in the percent of children who scored below the cutoff (≥ 2 standard deviations below the mean) used to identify potential cases of developmental delay on the primary outcome measure, the Ages and Stages Questionnaire (ASQ) (27.5% in 17-HPC vs. 28.0% in the vehicle group).

Team Leader Comments:

- ***The Applicant provided follow-up data on more than the 35-50% of the children that the FDA had specified as the minimal acceptable proportion of follow-up. The children followed were all at least 2.5 years of age, ranging up to 5 years of age.***
- ***The mean gestational ages of the children in Study 17P-FU were one week greater than those seen in the total cohort of 17-HPC and vehicle-exposed children in Study 17P-CT-002. The participants in the follow-up study may therefore represent a slightly lower risk group than the original population.***
- ***The rate of ASQ scores below the cutoff, signifying possible developmental delay, was higher in this study than would be expected based on normative data for the instrument. As vehicle-exposed children had a greater frequency of very low birthweight (<1500 gm) and delivery prior to 32 weeks, it would be expected that a higher proportion of vehicle-exposed children would be at risk for developmental delays on the basis of these perinatal risk factors. The classification of equal proportions (about 28%) of children in each group as possibly delayed suggests that the 17-HPC group also resembled an "at risk" group, albeit not as strongly attributable to low birthweight and gestational age. The Applicant did not conduct an analysis adjusting for these risk factors in assessing the proportion of possibly delayed children in each treatment group.***
- ***Based on this small number of children and the other assessments, there is no suggestion of adverse effects on postnatal development in the children whose mothers had been treated with 17-HPC during their pregnancy. There is also no indication that maternal treatment with 17-HPC resulted in any beneficial effect on early childhood development despite the prolongation of pregnancy and decrease in the rate of preterm birth; however, the study was not powered to detect such an effect.***

2.2.4 Recommendations of the Advisory Committee on Reproductive Health Drugs

The initial application was presented to the Advisory Committee on Reproductive Health Drugs (ACRHD) on August 29, 2006. A majority of committee members voted that prevention of preterm birth <35 weeks was an adequate surrogate for a reduction in fetal/neonatal mortality and neonatal morbidity; the vote was nearly unanimous that prevention of preterm birth <32 weeks was an adequate surrogate. Few committee members found prevention of preterm birth <37 weeks to be an adequate surrogate. A majority of members voted that the data submitted provided substantial evidence that 17-HPC prevents preterm birth at <35 weeks; a majority felt that there was not substantial evidence for effectiveness at <32 weeks. The Committee voted unanimously that further study was needed to evaluate the potential association of 17-HPC with second trimester miscarriage/stillbirth; the majority believed that this could be studied post-approval. The Committee also voted unanimously that a post-approval clinical trial or trials be conducted for further investigation of safety and effectiveness. Issues to be addressed in such a mandatory post-approval study included evaluation of the possible increased risk of miscarriage/stillbirth, assessment of possible

maternal complications, and elucidation of PK and pharmacodynamic (PD) properties of 17-HPC. In addition, long-term follow-up (including reproductive development/function, fertility and carcinogenic potential of 17-HPC) would need to be obtained in a subsequent study or perhaps through use of a registry.

Team Leader Comment:

- ***The data presented to the Advisory Committee for the rate of preterm birth at <32 weeks did not demonstrate statistical significance. Subsequent review and analysis by the FDA Statistical Reviewer confirmed that the treatment effect of 17-HPC at <32 weeks was statistically significant. However, further analysis also elucidated that the significant result at <32 weeks may have been driven by a single center, which enrolled a disproportionate number of and racially non-representative subjects.***

2.2.5 Conclusions of First Cycle Review

In the initial consideration of NDA 21-945, a major review issue was whether reliance for approval upon a single study that used a primary endpoint that is a surrogate for neonatal morbidity and mortality was justified. The clinical and statistical reviews raised questions as to whether the evidence of efficacy from this single study was convincing and compelling. The statistical reviewer, Lisa Kammerman, Ph.D., concluded in her review dated October 19, 2006, that

> *From a statistical perspective, the level of evidence from Study 17P-CT-002 is not sufficient to support the effectiveness of 17P. The primary reason is the absence of a second, confirmatory study. Without a second study, the generalizability of the study results to a larger population cannot be assessed.*

The clinical trial data did not provide evidence of a clinically meaningful or statistically significant effect on neonatal morbidity or mortality, as measured by a composite secondary endpoint. However, the trial did succeed in demonstrating efficacy of 17-HPC in preventing preterm birth at <35 and <32 weeks of gestation, cutpoints which the majority of members of the ACRHD believed represented adequate surrogates for fetal/neonatal mortality and neonatal morbidity. There remained some uncertainty as to whether the demonstrated benefit of 17-HPC in prevention of preterm birth at <32 weeks was due largely to the findings from a single large study site, or whether this result would be generalizable. There was also concern that the higher-than-expected rate of preterm delivery in the placebo arm of the study might be a large factor in the efficacy demonstrated for 17-HPC.

In addition to lack of data on long-term safety of prenatal exposure, the clinical data suggested that there may be more immediate safety issues, particularly involving increased early fetal loss in women treated with 17-HPC, a finding that mirrors nonclinical data relating high doses of 17-HPC with increased embryolethality in mice, rats and monkeys. The increased early loss in the 17-HPC arm offset a decreased number of neonatal deaths, with the result that treatment with 17-HPC provided no net survival benefit.

Therefore, the Division concluded that, while the Applicant had demonstrated efficacy of 17-HPC in a single trial in reducing the risk of preterm birth at gestational ages that correlate with increased neonatal morbidity and mortality, these data were not sufficiently robust to support approval. Deficiencies were also identified in the Pharmacology/Toxicology and Chemistry, Manufacturing and Controls information provided in the submission.

An Approvable letter was issued October 20, 2006 that defined additional information required to obtain approval to market 17-HPC. The following deficiencies and possible remedies were outlined in the letter:

Clinical

1. Further study is needed to provide confirmatory evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly, or through a well-established surrogate, such as the rate of preterm birth prior to 35 and 32 weeks of gestation.

2. There are insufficient data to evaluate a potential association of hydroxyprogesterone caproate (HPC) with increased risk of early fetal loss (second trimester miscarriage and stillbirth).

Information needed to address the clinical deficiencies

1. Submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of HPC for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510. If a placebo-controlled trial is determined not to be feasible, provide alternative study design proposals.

2. Provide a draft protocol to evaluate the potential association of HPC with increased risk of second trimester miscarriage and stillbirth. This could be assessed as a part of the confirmatory efficacy study referred to in Item No. 1 above.

Pharmacology and Toxicology

There is a lack of nonclinical data from a multi-generational reproductive toxicology study for this product.

Information needed to address the toxicology deficiency

A GLP-compliant, multigenerational reproductive toxicology study needs to be performed, evaluating all stages of pregnancy during which dosing will be administered in humans. The study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including learning, behavior and reproductive function, in offspring exposed *in utero*. At the time of a Complete Response submission to this approvable letter, provide, at a minimum, an unaudited interim final report of the requested study.

Chemistry, Manufacturing and Controls (CMC)

1. Significant degradation was observed for the light-stressed drug product sample with respect to content (assay) during the HPLC method validation studies. Thus, the drug product appears to be photosensitive; however, the resulting photodegradation products are not detectable by your HPLC method.

2. Given the results from your photostability study in which both the Stage 1 (fully exposed to light) and Stage 2 (enclosed in a chipboard box) samples showed decreases in content (assay) from that of the control (wrapped in foil) without corresponding increases in impurities by your HPLC method, you have not demonstrated that the secondary packaging provides adequate light protection for the drug product.

3. Your proposed expiration date of 24 months for the drug product is not acceptable based on the stability data included in your application to date.

Information needed to address the CMC deficiencies

1. Since you cannot account for the degradation of the active ingredient under light-stress conditions by your HPLC method, you should develop a supporting method that can adequately detect and quantitate the potential photodegradation products. The drug product specifications should include limits for any potential impurities observed using the new method, and a detailed description of the new analytical procedure with appropriate validation should be provided.

2. Alternative primary and/or secondary packaging should be used to protect the drug product from light. A description and justification for the new packaging system should be submitted with appropriate letters of authorization. In addition, you should revise the drug product labeling to state that the vials should be protected from light.

3. Based on the limited stability data provided in the application and the out-of-specification (OOS) results for particulate matter observed at accelerated conditions, an expiration date of NMT (b) (4) would be appropriate for the drug product when stored at controlled room temperature, protected from light. You are encouraged to determine the cause of the OOS results for particulates under accelerated conditions, and if necessary, you should consider a different container closure for storage of your drug product.

Additional issues that would need to be addressed postmarketing, if the product were to be approved:

Clinical

1. Completion of the additional efficacy and safety study(ies) requested above under the description of clinical deficiencies will be required as a condition of an approval under Subpart H 21 CFR 314.510 (Item No. 1 above under clinical deficiencies) or as a formal phase 4 commitment (Item No. 2 above under clinical deficiencies).

2. Long-term post treatment safety data (at least through puberty) from children whose mothers had been treated with HPC is lacking in the NDA. This information is requested and could be obtained through the establishment of a surveillance program (e.g., registry) to evaluate the effects of prenatal exposure in adolescents and young adults. Submit your proposal as to how these data would be obtained.

3. Additional developmental assessment is needed of children at ages 18-24 months whose mothers had been treated with HPC. This assessment could be obtained from the offspring of women enrolled in the confirmatory efficacy study or the safety study addressing early fetal loss. Children who screen positive for developmental delay should have a formal psychometric assessment and an additional assessment by a neurologist.

Clinical Pharmacology

In planning your subsequent clinical trial(s), the following pharmacokinetic elements should be considered as part of the design to allow for better understanding of HPC pharmacokinetics and optimal dosing:

- Characterize the pharmacokinetics of HPC and its metabolites in pregnant women (including both plasma and urine concentrations) at several periods throughout the pregnancy.
- Assess the HPC exposure-response relationship and the effect of body weight on the pharmacokinetics of HPC via sparse sampling of all subjects.
- Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on HPC pharmacokinetics.

Following receipt of the Approvable letter, the Applicant filed a Formal Dispute Resolution Request to the Office of Drug Evaluation III (ODE III) on March 16, 2007. Three requirements in the Approvable letter were disputed: the reproductive toxicology study, the multicenter confirmatory efficacy trial, and the preapproval submission of a protocol to evaluate potential increased risk of early fetal loss. Dr. Daniel Shames of ODE III reviewed the Applicant's arguments and wholly concurred with the Division's decisions. This was conveyed to the Applicant on April 13, 2007.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Barbara Wesley, stated in her review of the current application dated January 23, 2009:

This reviewer recommends a complete response (approvable) action for Gestiva (17α-hydroxyprogesterone caproate [hereafter referred to as 17-HPC, but also known as HPC and 17P]) for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth.

Team Leader Comment:

- ***I concur with Dr. Wesley's recommendation.***

Dr. Wesley further noted:

This reviewer agrees with the overall design of the draft Protocol (hereafter referred to as the "Confirmatory Study") submitted by the Applicant on January 15, 2009, that is designed to:

1. *Confirm one of the previous findings of efficacy in Study 17P-CT-002 (i.e., a reduction in preterm births at < 35^0 weeks of gestation),*
2. *Obtain further information regarding the effect of treatment with hydroxyprogesterone caproate (HPC) on neonatal morbidity and mortality, and*
3. *Address the concern regarding early pregnancy loss identified in our Approvable letter of October 20, 2006.*

In addition, the Applicant has provided a draft protocol for a follow-up study of offspring up to two years of age in the U.S. and in other countries.

Dr. Wesley concluded:

> *This reviewer is concerned that health care providers and Institutional Review Boards, particularly in the U.S., may be reluctant to conduct randomized, placebo-controlled trials of 17-HPC for PTB [preterm birth] prevention as a result of th[e] recently published ACOG Committee Opinion.*
>
> *To provide reassurance that these critical studies are conducted, the following is recommended as a condition for approval under Subpart H:*
>
> - *Obtain IRB approval from approximately 15 research centers (both U.S. and non U.S.) to enroll the target number of 1707 subjects. This recommendation takes into consideration that the applicant may need to make changes (add or subtract sites) at a later time.*
> - *Enroll a minimum of 5% of planned subjects (85 subjects [5% of 1707 subjects]); a minimum of 15 subjects should be enrolled from U.S. sites. No site should ultimately enroll more than 15% of all subjects.*

Team Leader Comment:

- ***I generally concur with Dr. Wesley's recommendation. My slightly more detailed description of the elements needed to address the deficiencies of this application is outlined in Section 13.1.***

Finally, Dr. Wesley recommended the following phase 4 commitments:

1. *The completion of the "Confirmatory Study" described above. This study will need to be initiated prior to approval but will be completed post-approval under Subpart H.*
2. *The completion of the randomized, double blinded, controlled trial to evaluate developmental and safety issues of the offspring from the Confirmatory Study*

Team Leader Comment:

- ***I concur that the Applicant will need to complete the confirmatory efficacy study post-approval as a condition of Subpart H approval, and that the Applicant will need to conduct and complete the offspring follow-up study post-approval.***

3. CMC/Device

The primary Chemistry Reviewer, Donna Christner, Ph.D., made the following recommendations in her review dated December 22, 2008:

> *This NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. All facilities involved are in compliance with cGMP, and labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for APPROVAL.*

There were no recommendations for post-marketing commitments or risk management steps.

Labeling recommendations made by Dr. Christner were incorporated into the labeling revisions proposed by the Division.

3.1 General product quality considerations

The drug substance and drug product information was reviewed and found acceptable in the original review NDA 21-945, and no CMC changes were proposed in this Complete Response. Three CMC deficiencies were conveyed in the Approvable letter dated October 20, 2006:

- Develop a supporting method that can adequately detect and quantitate the potential photodegradation products
- Provide a description and justification for new packaging system to protect the drug product from light; revise the product labeling to state that vials should be protected from light
- Determine the cause of the out-of-specification results for particulates under accelerated conditions and, if necessary, consider a different container closure system

The Applicant submitted additional data regarding the potential for photodegradation, and the Division agreed in a teleconference on January 11, 2007 that there was no increase in photodegradants and therefore no need to develop additional tests, and that photosensitivity of the product would be addressed with package labeling. For the third point, the Applicant provided adequate information about the particulate matter found in the stability samples held under accelerated conditions (see Section 3.3).

3.2 Facilities review/inspection

The Office of Compliance issued an ACCEPTABLE overall recommendation for all the facilities involved.

3.3 Other notable issues (resolved or outstanding)

Late in the review cycle, the Applicant informed the Division that, due to errors in calculation, the reported particulate matter results were 10-fold lower than the actual values. As substantial new data were submitted for review, the submission was coded as a major amendment, and the review clock was extended by 90 days. The new data included both corrected calculations and additional stability data (up to 30 months on the primary stability batches and 24 months on the process validation batches). The particulate matter values were well within specification, albeit higher than originally reported, and the information was found to be acceptable.

An additional issue was raised regarding microbiological stability once the product vial was penetrated. This was satisfactorily resolved (see Section 6) and the data found to support an in-use shelf life of five weeks after initial penetration of the vial.

4. Nonclinical Pharmacology/Toxicology

As noted, one of the primary deficiencies in the initial application concerned insufficient preclinical data to support approval; specifically, lack of a multigenerational reproductive toxicology study. Published studies[5,6] reviewed in the initial cycle dosed pregnant Wistar rats on gestational days 1, 7 and 14, using intraperitoneal doses of 10 and 25 mg/kg. These data demonstrated decreased sperm motility, viability and count in the F_1 male generation, as well as a reduction in implantation sites and viable fetuses when F_1 males were mated with naïve females. The relevance of the study findings to human males exposed *in utero* to 17-HPC were questioned on the grounds of insufficient numbers of animals, use of unconventional species, different route of administration, lack of any PK/ADME data, lack of correlation

[5] Pushpalatha et al. Naturwissenschaften 91: 242-4, 2004

[6] Pushpalatha et al. Naturwissenschaften 92: 385-8, 2005

between gestational timing of exposure and expected timing of human exposure and lack of developmental studies in exposed offspring.

However, in the absence of well-controlled preclinical data, these published data raised concerns about adverse effects on exposed offspring. The Approvable letter dated October 20, 2006 stated:

> *A GLP-compliant, multigenerational reproductive toxicology study needs to be performed, evaluating all stages of pregnancy during which dosing will be administered in humans. The study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including learning, behavior and reproductive function, in offspring exposed in utero. At the time of a Complete Response submission to this Approvable letter, provide, at a minimum, an unaudited interim final report of the requested study.*

The current submission included such a study, which was audited by FDA inspectors and found acceptable. This study in Sprague-Dawley rats included reproductive phases 1 and 2 and a teratology phase, with dosing occurring on gestational days 8, 14 and 20; 17; and 6, 12 and 18, respectively. Phase 1 and 2 were designed to demonstrate effects of dosing before (phase 1) and after (phase 2) gametogenesis. Doses of 0 (vehicle control), 5, 25 and 150 mg/kg/dose were used. The study did not show any adverse effects on the health of dams, fetuses, offspring or second generation offspring. Specific findings included:

- No adverse effects on any F_1 fertility parameters or on the F_2 sex ratio or viability index (phase 1)
- No adverse effects on sperm percent motility, count or concentration, or percent abnormal (phase 1 and phase 2)
- No adverse effects on delivery (phase 2)
- Dose-related increase in traumatic lesions of the feet in offspring from medium and high dose groups. However, the pharmacology/toxicology reviewer accepted the Applicant's argument that these were not treatment-related, as these lesions did not occur in offspring of phase 1 animals, which received more injections.
- Comparable physical, developmental and behavioral evaluations of F_1 pups from control and all dose groups
- NOAEL of 150 mg/kg/dose

In addition a PK study was also conducted in Sprague-Dawley rats, using 5 or 150 mg/kg on gestational day 5. This demonstrated a T_{max} of 24 hours and a $T_{1/2}$ of about six days.

The primary Toxicology Reviewer, Alex Jordan, Ph.D., with concurrence by Team Leader Lynnda Reid, Ph.D., made the following recommendations in his review dated October 14, 2008:

> *Recommendations on approvability: I recommend approval of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth.*
>
> *Recommendations for nonclinical studies: None*
>
> *Recommendations on labeling: Under Pregnancy: The pregnancy category should be changed from A to B.*

Additional labeling recommendations made by Dr. Jordan were also incorporated into the labeling revisions proposed by the Division.

5. Clinical Pharmacology/Biopharmaceutics

The original NDA submission was found acceptable by Clinical Pharmacology in 2006, and no new clinical pharmacology studies were submitted in the Complete Response. Two new literature reports on the metabolism of 17-HPC support the previous finding that the caproate ester remains intact as 17-HPC is metabolized. One report mentioned in-press results of an *in vitro* study showing that 17-HPC and its metabolites enter the fetal circulation.

Very limited PK data available at the time of the original submission demonstrated a C_{max} of about five days, and a $T_{1/2}$ of almost eight days. An *in vitro* enzyme inhibition study showed that 17-HPC slightly inhibited (by <40%) CYP2C8, CYP2C9 and CYP2C19, and inhibited CYP3A4 by almost 50%.

The Approvable letter of October 20, 2006 contained three Clinical Pharmacology issues to be addressed post-marketing; the Sponsor has attempted to address these in the protocol for the proposed confirmatory efficacy and safety study or by submitting results from an ongoing NIH PK study.

The primary Clinical Pharmacology Reviewer, Doanh Tran, Ph.D., stated the following in his review dated August 26, 2008 and in an addendum to the review, dated January 15, 2009:

> *The Office of Clinical Pharmacology/Division of Clinical Pharmacology III finds NDA 21-945 acceptable provided the labeling comments and Phase IV commitment requests are adequately addressed.*

The following phase 4 commitments were requested in the addendum to the review:

- *The sponsor will provide data characterizing the pharmacokinetics (PK) of 17 α-hydroxyprogesterone caproate (17-HPC) and its metabolites in plasma and urine in pregnant women throughout different gestational stages.*
- *The sponsor will conduct an in vitro study using human hepatocytes to determine whether 17-HPC induces or alters the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.*

Team Leader Comment:

- ***The information described in these bullets would be requested as a phase 4 commitment if approval were granted in the next review cycle. The Applicant may be able to obtain the requested information for bullet 1 from published results from an ongoing NIH study at the University of Pittsburgh or may need to conduct an additional PK study to comply.***

Labeling recommendations made by Dr. Tran were incorporated into the labeling revisions proposed by the Division.

6. Clinical Microbiology

Clinical microbiology consults were submitted on June 19, 2008 and December 18, 2008. In the initial response, the reviewer, John Metcalfe, Ph.D., reviewed a major amendment made to the submission (change in (b) (4)), and recommended approval on the basis of microbiological product quality. He noted that

The proposed changes to the (b) (4) *sequence do not adversely affect the microbiological quality of the subject drug product. No additional* (b) (4) *retention validation studies are necessary since there are no changes to the* (b) (4)

Further review of the submission resulted in a request that the Applicant justify the requested five-week shelf life following the initial penetration of the multiuse vial. Cytyc provided data using the USP <51> Antimicrobial Effectiveness Testing method. The reviewer, James McVey, Ph.D., noted that

The preservative has better activity against Candida albicans after 30 months at room temperature than it did initially. Activity against Aspergillus niger is questionable but the test only requires stasis for the fungi so the product passes this test.

Dr. McVey recommended Approval of the product and concluded that the preservative system is adequate for the product's labeled use period after initial penetration of the vial.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

To address the clinical issues in the Approvable letter of October 20, 2006, the Applicant's Complete Response contained the protocol for a confirmatory efficacy and safety study, along with a discussion of the likely feasibility of conducting the study. The Applicant also provided a draft protocol for an infant follow-up study, and a discussion of a proposed follow-up study of exposed offspring once they reached adolescence.

7.1.1 Confirmatory Efficacy and Safety Study

The Applicant provided an initial protocol in the Complete Response, and subsequently submitted two revisions in response to comments made by the DRUP Clinical and Statistical reviewers. The description of the protocol in this review is based upon the final revision submitted electronically on January 15, 2009. The Applicant plans a multicenter, randomized, double-blind, vehicle-controlled study of 17-HPC for the prevention of preterm delivery in women with a previous singleton spontaneous preterm delivery. The study will enroll 1,707 women aged 16 and above with a singleton gestation, in a 2:1 ratio, stratified by study site, to 17-HPC or vehicle (hereafter referred to as placebo). Subjects will receive weekly injections of study drug from randomization at 16^0 to 20^6 weeks of gestation up through 36^6 weeks or delivery. The same dose and formulation of 17-HPC used in Study 17P-CT-002 will be utilized. The vehicle will also be the same as that used in the previous study.

The primary objective of the study is to determine whether 17-HPC reduces the rate of preterm delivery prior to 35^0 weeks as compared to placebo. The key secondary objective is to determine whether 17-HPC reduces the rate of neonatal morbidity/mortality, as measured by a composite index, as compared to placebo. This will be assessed in a hierarchical manner, to protect the type 1 error, only if the primary endpoint of delivery < 35 weeks attains statistical significance. The elements of the neonatal morbidity/mortality index are:

- Neonatal death
- Grade 3 or 4 intraventricular hemorrhage (IVH)
- Respiratory distress syndrome (RDS)

- Bronchopulmonary dysplasia (BPD)
- Necrotizing enterocolitis (NEC)
- Proven sepsis

Additional secondary objectives include:

- Exclusion of a doubling of the risk of fetal/early infant death or stillbirth in the 17-HPC arm as compared to placebo
- Determination as to whether 17-HPC reduces the rate of preterm delivery prior to 32^0 weeks as compared to placebo
- Determination as to whether 17-HPC reduces the rate of preterm delivery prior to 37^0 weeks as compared to placebo
- Determination as to whether 17-HPC reduces the rate of stillbirths (including fetal losses) from 20 weeks of gestation on, as compared to placebo
- Determination as to whether 17-HPC reduces the rate of neonatal death as compared to placebo
- Evaluation of PK/PD parameters for 17-HPC in a subset of 450 subjects stratified by BMI

Eligible subjects will be women aged 16 years and above with a history of a prior spontaneous preterm delivery, with a current singleton pregnancy dated at the time of randomization at 16^0 through 20^6 weeks of gestation by ultrasound. Ultrasound between 14^0 and 20^3 weeks of gestation will be required to rule out fetal anomalies, which are exclusionary. Women with a history of thromboembolic disease, seizure disorder, hypertension requiring medication, current or planned cerclage, or taking heparin will also be excluded.

Subjects will receive a trial injection of placebo prior to randomization to evaluate for compliance and tolerability of the injection. Maternal subjects will be followed until the later of 30 days after last dose of study drug or discharge from the delivery hospitalization, and neonates will be followed until 28 days of life, with those remaining hospitalized at 28 days to be followed until the earlier of discharge or 120 days of life. Maternal subjects who discontinue study drug will remain on study, and, at a minimum, delivery outcome data will be obtained. A subject lost to follow-up will have the last date known pregnant noted for the analysis.

The proposed sample size will provide 98% power to detect a 30% reduction (30% to 21%) in the rate of preterm birth at <35 weeks with an alpha level of 0.05%. The study will also have 90% power to detect a 35% reduction (17% to 11%) in the rate of the composite neonatal index, allowing for fetal loss occurring in 2.5% of the pregnancies. The power to rule out a doubling of risk of fetal/early infant death, assuming a rate of 4%, is 83%.

The percent of subjects with preterm birth at <35 weeks will be determined as the point estimate of the survival function from a staggered entry Kaplan-Meier analysis, to account for gestational age at entry. A two-sided 95% confidence interval (CI) for the relative risk of fetal/early infant loss will be calculated by the Cochran-Mantel-Haenszel method stratifying for gestational age at entry. A doubling of the risk of fetal/early infant loss will be ruled out if the upper bound of the 95% CI is ≤ 2.0.

Team Leader Comments:

- ***The objectives and key endpoints were revised in accordance with comments made by the clinical and statistical reviewers, and are acceptable.***
- ***The inclusion of a clinical endpoint, the neonatal morbidity/mortality index as a key endpoint, analyzed in a hierarchical manner, will address the Subpart H goal of extending initial findings based on surrogate endpoints to demonstration of an actual clinical benefit.***
- ***The anticipated reduction in the <35 week delivery endpoint used to power the study is based on the results of Study 17P-CT-002 and appears reasonable. Similarly, the rates of having a component of the neonatal index and of fetal/early infant death are based on Study 17P-CT-002 results.***
- ***The analysis accounting for gestational age at the time of randomization will help address concerns arising from the exploratory analyses by the FDA Statistical Reviewer in the first review cycle that suggested there might be an effect of the time of treatment initiation on efficacy.***
- ***Dr. Lisa Kammerman, the FDA statistician who reviewed both cycles of the Gestiva application, indicated in her review addendum dated January 14, 2009 that she agrees with the changes made in the most recent protocol revision that address the statistical issues she raised in her review of the original protocol for the confirmatory study.***

Safety assessments will include determination of maternal AEs and protocol-defined pregnancy complications, including gestational diabetes, oligohydramnios, significant antepartum bleeding, preeclampsia and gestational hypertension, placental abruption and chorioamnionitis. Subjects will be asked a standard question to elicit AEs at each weekly visit.

Fetal/early infant death/stillbirth is defined to include

- Delivery from 16^0 through 19^6 weeks of gestation (spontaneous abortion/miscarriage)
- Death occurring in previable liveborns (<24 weeks of gestation)
- Ante- or intrapartum death from 20 weeks of gestation through term (stillbirths)

Standard assessments to work up the etiology of fetal/early infant deaths will be utilized, including perinatal autopsy and placental pathology.

7.1.2 Evidence of Feasibility

The Applicant initially submitted as evidence of feasibility a survey of Ob/Gyns and Maternal Fetal Medicine specialists that sought to determine their willingness to participate in a placebo-controlled trial of 17-HPC following FDA approval. Participants were also asked whether they anticipated that their Institutional Review Board (IRB) would have concerns about such a study and whether they anticipated that eligible patients would be willing to enroll. Of 325 surveys disseminated, 67 physicians responded (response rate 21%) and of these, 33 (49%) indicated willingness to participate in such a trial.

Given the low response rate and small absolute number of physicians willing to participate, the Division asked the Applicant to provide greater assurance that a post-approval placebo-controlled trial could actually be conducted in the U.S. The Applicant submitted a response on September 3, 2008 following further discussion with key opinion leaders in Ob/Gyn and with those physicians who had indicated wiliness to participate at the time of the original survey. Among the 33 potential participants, the Applicant obtained letters of interest from 11 considered to be prominent investigators in academic settings, military bases or large private

practice groups. The Applicant also identified several obstetric researchers at Canadian academic centers who expressed interest in the study.

During the course of this review cycle, the ACOG issued a revised Committee Opinion on Use of Progesterone to Reduce Preterm Birth[7]. The new opinion was in contrast to the 2004 statement that stated

> *When progesterone is used, it is important to restrict its use to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug.*

The 2008 opinion states

> *Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes.*

Team Leader Comment:

- ***I interpret this new statement as establishing a de facto standard for care for women with a previous spontaneous preterm birth. There is little to no acknowledgement of the outstanding issues with regard to determining the safety and efficacy of 17-HPC in the 2008 opinion. This may make it extremely difficult for a physician to enroll patients into a placebo-controlled study. In addition to treating physicians' concerns about potential liability, this statement may give rise to ethical concerns by IRBs. The informed consent would likely need to notify patients of the ACOG opinion, and it is difficult to imagine a substantial portion of high-risk women who read this statement being willing to consent to possible placebo allocation.***

Due to concerns about the impact of the recent ACOG opinion on the feasibility of the study, the Division held a teleconference with the Applicant on November 19, 2008. The Applicant was informed that the Division did not believe that letters of intent to participate in a post-approval study, written prior to issuance of the new ACOG opinion, would provide sufficient evidence of feasibility of the confirmatory study. The Applicant recontacted the original 33 survey respondents who had indicated willingness to participate to see whether their interest had been adversely affected by the ACOG opinion. Working over a short time interval, the Applicant received responses from 16 potential investigators, 12 of whom continued to be interested. Four indicated that they no longer believed the study could be conducted in the US. The Applicant also identified 16 additional US investigators who expressed interest in participating, and 16 foreign investigators, from Canada, Mexico, and Western Europe. In total, the Applicant believes that 55 investigators at 46 sites in nine countries are likely to participate.

Team Leader Comments:

- ***The Applicant was able to document only that 12 of the original 33 potential investigators remained willing to participate. One quarter of those who responded to the new query indicated that the ACOG statement had led them to reconsider their involvement in the study and that they would no longer participate.***
- ***As noted above, the ACOG opinion raises concern that the study could fail on any of three levels required for success: investigator participation, IRB approval and patient enrollment. While the Sponsor has provided some reassurance that there remain US***

[7] ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 419, October 2008

physicians willing to participate in the trial, the information provided in the current application does not address the probability of IRB approval or of patient enrollment. These can only be addressed by actual initiation of the trial.

The Division agreed, in a teleconference on December 18, 2008, that a multinational trial would be acceptable, although inclusion of US and Canadian sites was requested. The Division continued to request that evidence of feasibility must be demonstrated on all three levels (investigators, IRBs and patients).

Team Leader Comments:

- ***While countries outside the US do not appear to be utilizing compounded 17-HPC as extensively as the US, FDA approval (and perhaps even statements by the ACOG) is given considerable deference by some other countries. I am not entirely convinced that barriers to enrollment of US patients may not also affect potential enrollment in some other countries. Therefore, I believe that to demonstrate that the confirmatory efficacy and safety trial will indeed be feasible, the Applicant must actually initiate enrollment before the Division could take an Approval action on 17-HPC.***
- ***I would not require completion of the study, or even submission of any interim data, for the next review cycle. I would find a Complete Response sufficient if it documented:***
    - ***Enlistment of investigators at a sufficient number of US and international sites to ensure ultimate enrollment of 1,700 subjects, with no site to enroll more than 15% of the total number of subjects, and with at least 10% of the sample to be from the US and Canada***
    - ***IRB approval at a sufficient number of sites to ensure ultimate enrollment of 1,700 subjects, with no site to enroll more than 15% of the total number of subjects***
    - ***Enrollment of at least 5% of the anticipated sample size***
    - ***Enrollment of at least ten subjects at US study sites (this is based roughly on enrollment of at least 5% of the US/Canadian subjects; since the greatest difficulty in enrollment is expected to be in the US, assurance that a minimum number of US subjects can be enrolled is required)***

7.1.3 Evaluation of Follow-up Study Proposals

In the Approvable letter, the Division had requested additional developmental assessment of children at ages 18-24 months whose mothers had been treated with HPC, including a formal psychometric assessment and an additional assessment by a neurologist for children who screen positive for developmental delay. In response, the Applicant provided an initial protocol for a non-interventional follow-up study of exposed offspring of mothers who participated in the confirmatory efficacy and safety study. The study will enroll 375 children (250 exposed *in utero* to 17-HPC and 125 to placebo) aged 18-24 months to determine whether there is a difference in the attainment of developmental milestones. Children will be evaluated using the Ages and Stages Questionnaire (ASQ), the same instrument used for screening in Study 17P-FU. Those who score positive for developmental delay in one or more of the five ASQ domains will be referred for further secondary evaluation (e.g., Bayley Scales of Infant and Toddler development, neurological exam, Gross Motor Function Classification System and Modified Checklist for Autism in Toddlers). The proposed sample size is sufficient to provide 88% power to detect a 15% absolute difference in the rate of screen-positive subjects on at least one of the ASQ domains, based on an alpha level of 0.05 and an expected rate of 30% in the 17-HPC group.

Team Leader Comments:

- ***The anticipated rate of screen-positive subjects in the 17-HPC was based on findings from Study 17P-FU, which found 28% were screen-positive for developmental delay on at least one domain of the ASQ. The proposed sample size is 25% greater than that in Study 17P-FU.***
- ***The original follow-up Study 17P-FU was reviewed by a pediatric expert, (b) (4) (b) (4) during the first cycle. A number of her criticisms of the earlier study, including failure to follow-up screen-positive subjects with further appropriate evaluations and lack of neurological evaluations, have been addressed in the current protocol.***
- ***The submitted protocol is in draft form, and would need to be finalized and reviewed in the next cycle submission. Conduct of the study would then be required as a phase 4 requirement. The Division has requested that the Applicant seek to obtain consent to be recontacted for follow-up from all women eligible for enrollment in the confirmatory efficacy and safety study. From the pool of women who consent, formal consent for their child to participate in the follow-up study would be sought in the future, in a subset of sufficient size to provide a pool of 375 children who complete the ASQ assessment.***

The Applicant also discussed conducting a long-term post-treatment safety study; this was in response to the Division's request in the Approvable letter for long-term post-treatment safety data at least through puberty of exposed offspring. The Applicant proposed to conduct a retrospective cohort analysis of 17-HPC-exposed adolescents at age 15, with the population to be defined through the use of electronic longitudinal medical records, such as those maintained by large health maintenance organizations, claims databases or large healthcare payers. Outcomes would be based on healthcare utilization and diagnoses using standard medical coding found in the medical records; individual subjects would not be identifiable and confirmatory chart review would not be possible.

Team Leader Comment:

- ***The Division's original request for a long-term safety study was prompted in large part by the worrisome results concerning fertility and reproductive performance in the Pushpalatha nonclinical studies. Given the reassuring results of the new GLP-compliant reproductive toxicology study, I feel less compelled to require such an adolescent study. If results of concern should be obtained in the infant/toddler follow-up study, the Division might decide to request a longer-term follow-up study under its FDAAA authorities, based on identification of a new safety signal. However, at this time, I would not recommend that an adolescent study be required as a phase 4 commitment.***

8. Safety

8.1 SAFETY FINDINGS

A summary of the safety findings from the original submission is presented in Section 2.2.3. No new clinical data were contained in this current submission.

8.1.1 Safety Update

A 120-day Safety Update Report was not submitted; the Applicant had no ongoing 17-HPC clinical studies at the time of the Complete Response submission and has conducted no new 17-HPC clinical trials.

The Division of Adverse Event Analysis II provided an update on adverse events reports submitted to the AERS system since the previous review done in August 2006. Six unique case reports were identified, three relating to preterm labor and one each of maternal syncope, maternal depression and congenital heart defect in an exposed infant.

8.1.2 Postmarketing Safety Findings

No country in the world has approved 17-HPC for marketing; thus, there are no postmarketing safety data. The primary review by Dr. Barbara Wesley contains a review of current literature.

8.1.3 Overall Assessment of Safety Findings

The safety concerns noted in the first cycle review remain pertinent. The proposed confirmatory efficacy and safety study will evaluate possible increased risk of early fetal loss and certain maternal complications.

9. Advisory Committee Meeting

As noted, an Advisory Committee was held in the first review cycle. This Complete Response application was not taken to an Advisory Committee.

10. Pediatrics

The Applicant requested a full waiver of pediatric studies, and the Division concurred, as studies would be impossible or highly impractical because there are too few children with the condition to study. The Pediatric Review Committee (PeRC), on December 31, 2008, agreed to a partial waiver for premenarchal females, and to extrapolate efficacy for postmenarchal females.

11. Other Relevant Regulatory Issues

No financial disclosure information was submitted, since no clinical data were provided.

During the first cycle review, site inspections at the three highest-enrolling sites were requested, but only one was completed during the review cycle. Inspection reports were subsequently provided for the Universities of Tennessee and Utah, both of which received Voluntary Action Indicated (VAI) reports. However, Roy Blay, Ph.D. concluded in his review dated January 10, 2007 that none of the regulatory violations noted appeared to have a significant impact on data reliability or patient safety, and that the data appeared acceptable to support the indication.

An audit of the non-clinical reproductive toxicology study site at (b) (4) was requested of the Division of Scientific Investigation (DSI), in part because of the very different results of the submitted study and the published studies by Pushpalatha et al. In addition, the inspection evaluated corrective actions undertaken following an earlier inspection in April 2007. The findings of the Good Laboratory Practices (GLP) inspection were that:

- The low dose (5 mg/kg/dose) groups in the reproductive phase 1 and teratology phase had much lower concentrations of test article than intended, outside the acceptance criterion of +/- 15%. There was no explanation for the out-of-specification result, which affected only the low dose group.
- Not all effects were dose-related: the F_1 male fertility index was lower in the mid- than the high-dose group; the body weights of F_2 male and female pups were lower in the high-dose groups. Both of these parameters were within the ranges found in historical background data at (b) (4)

- Appropriate corrective actions in response to deficiencies noted during the previous inspection were taken.

No Form 483 was issued; the audit was classified as No Action Indicated (NAI). Overall, there were no other deficiencies that would affect acceptance of the (b) (4) data. No explanation for the difference in results from this study as compared to the Pushpalatha data was proposed beyond use of different rat strains and different days of first dosing.

12. Labeling

The trade name Gestiva was found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) on October 22, 2008. This decision was reached after the Applicant provided details about how Gestiva would be distributed using a (b) (4) This would minimize the likelihood of any name confusion between Gestiva and Sustiva, which was DMEPA's original concern with the name. The package insert and carton and container labeling was reviewed by DMEPA on November 24, 2008, and comments were conveyed to the Applicant.

The Gestiva label was submitted in the format prescribed by the Physician Labeling Rule (PLR). A consult on the proposed label was obtained from the Study Endpoints and Label Development team. Their comments were incorporated into the label as appropriate. Labeling negotiations were not concluded in this cycle because the primary reviewers are not recommending approval.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that Gestiva receive a Complete Response action, based on the need for greater evidence of feasibility than what has been presented to date. Specifically, I recommend that the Applicant actually initiate the study prior to submitting the next Complete Response. The study would not need to be completed, nor would interim data need to be submitted in the Complete Response; thus, approval under Subpart H would be possible. However, sufficient enrollment to demonstrate the likely feasibility of completing the trial would be required. Acceptable evidence of feasibility would include the following elements:

- Enlistment of investigators at a sufficient number of US and international sites to ensure ultimate enrollment of 1,700 subjects, with no site to enroll more than 15% of the total number of subjects, and with at least 10% of the sample to be from the US and Canada
- Documentation of IRB approval at a sufficient number of sites to ensure ultimate enrollment of 1,700 subjects, with no site to enroll more than 15% of the total number of subjects
- Enrollment of at least 5% of the total anticipated sample size
- Enrollment of at least 15 subjects at US study sites (this is based on enrollment of approximately 10% of the expected number of subjects from the US and Canada; since the greatest difficulty in enrollment is expected to be in the US, assurance that a minimum number of US subjects can be enrolled is required)

With the Applicant's acceptance of the final Division-recommended revisions in the confirmatory efficacy and safety study protocol, the protocol is acceptable to the clinical and statistical reviewers. The final protocol for the infant/toddler follow-up study will need to be submitted for review in the next cycle. Label negotiations were initiated but not concluded in this cycle; these will need to reach resolution in the next cycle.

13.2 Risk Benefit Assessment

The public health importance of preterm birth and the lack of efficacious treatment of preterm labor must be considered in weighing the risk/benefit ratio for a drug proposed for the indication of prevention of recurrent preterm birth. However, it was concluded by both the clinical and statistical reviewers in the first cycle review that the primary trial (Study 17P-CT-002) did not meet the general requirements for acceptance of a single adequate and well-controlled trial to provide sufficient evidence of efficacy to support approval of 17-HPC for marketing. The clinical trial data did not provide evidence of a clinically meaningful or statistically significant effect on neonatal morbidity or mortality, as measured by a composite endpoint. The primary efficacy endpoint (delivery at <35 weeks of gestation), on which statistical significance was demonstrated, is a surrogate for neonatal morbidity/mortality. There also remains a question as to whether the benefit of 17-HPC in prevention of preterm birth at <32 weeks in Study 17P-CT-002 was largely attributable to a single study site, or whether this result generalizes. In addition, the clinical data suggested that there may be safety issues, particularly involving increased early fetal loss in women treated with 17-HPC.

In the present submission, the Applicant has presented an acceptable protocol for a confirmatory efficacy and safety study, which the Applicant proposes to conduct post-approval. However, in view of the recent ACOG statement, there is substantial concern as to whether the proposed study could be conducted in the US. ACOG's recommendation may be interpreted by many US physicians as establishing a standard of care for pregnant women with a previous spontaneous preterm birth, such that the possibility of randomization to placebo treatment might be considered unacceptable to IRBs, referring physicians, and patients. The Division has concurred in the Applicant's proposal that the study be conducted globally, including in the US. This will increase the likelihood that an adequate number of women can be enrolled and randomized and that the study will be successfully completed. However, I believe it remains crucial that some portion of the study be conducted in the US, and therefore the Applicant will need to demonstrate that it can enlist US physicians, that US IRBs will

approve the study, and that patients will consent to participate. This level of assurance of feasibility will require actually initiating the study prior to the Division's possible approval of 17-HPC for marketing under the conditions of Subpart H.

13.3 Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are recommended in this review cycle.

13.4 Recommendation for other Postmarketing Study Commitments

If Gestiva is approved for marketing under the conditions of Subpart H in a subsequent review cycle, it is likely that phase 4 requirements would include conducting the infant follow-up study and providing detailed data on the PK profile of 17-HPC in pregnant women and on the effects of 17-HPC on cytochrome metabolic activity.

13.5 Recommended Comments to Applicant

Extensive discussions with the Applicant have been held regarding the deficiencies of the current application; no further comments need to be conveyed other than those to be contained in the Complete Response letter as described previously in Section 13.1.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Soule
1/23/2009 12:15:59 PM
MEDICAL OFFICER

Scott Monroe
1/23/2009 02:13:53 PM
MEDICAL OFFICER
I concur with the recommendation of Dr. Soule that hydroxyprogesterone caproate not be approved at the present time for the prevention of preterm birth in women who have had a prior preterm birth.

DEPUTY OFFICE DIRECTOR MEMORANDUM

RE: Request for Formal Dispute Resolution of Approvable Action (October 20, 2006)

From: Daniel Shames MD, Deputy Director. ODE III, CDER/FDA

NDA	NDA 21-945
Type of Submission	Request for Formal Dispute Resolution
Applicant	Adeza Biomedical Sunnyvale, CA 94089
Proprietary Drug Name	Gestiva (proposed)
Established Drug Name	17 α-hydroxyprogesterone caproate Injectable (17HPC)
Drug Class	Progestogen
Indication	Prevention of preterm birth in women with a history of at least one spontaneous preterm birth
Route of administration	Intramuscular
Dosage Form	Injectable
Dosage Strength	17 α-hydroxyprogesterone caproate (250 mg/mL) in castor oil with 46% benzyl benzoate and 2% benzyl alcohol
Dosing Regimen	Once weekly injections of 17 α-hydroxyprogesterone caproate (250 mg in one mL) starting between 16 weeks 0 days and 20 weeks 6 days gestation to 37 weeks gestation or until birth
CDER Receipt Date	March 16, 2006
Date of Memorandum	April 13, 2006

1.0 Summary of Dispute

On April 26th, 2006, Adeza submitted NDA 21-945 to the Division of Reproductive and Urologic Products (DRUP) for 17HPC with the proposed induction of "Prevention of preterm birth in women with a history of at least one spontaneous preterm birth." The Division granted a priority review and held an Advisory Committee meeting on August 29th, 2006. On October 26th, 2006, DRUP wrote an Approvable Letter to Adeza communicating deficiencies and information required to address said defiencies before approval could be granted.

On March 16th, 2007, Adeza submitted a Formal Dispute Resolution Request to the Office of Drug Evaluation III regarding three specific scientific requirements stipulated by the Division in the Approvable Letter. The requirements being disputed are:

1. The requirement for a multi-generational reproductive toxicity study in animals.

The Division stated in the Approvable Letter "that at the time of a Complete Response submission to this approvable letter, provide at a minimum, an unedited interim final report of the requested { reproductive toxicity} study." Adeza believes that "During initial discussions with the Division regarding preclinical safety data, the Division stated that existing published data would be sufficient to support the NDA…consequently Adeza did not initiate any preclinical studies." In addition, Adeza believes that "substantive and relevant toxicology studies were provided to the NDA and subsequent amendment to the

NDA." Therefore, the Adeza believes that **this reproductive toxicology study is not required for approval.** However, **"if the dispute resolution process determines that a rodent study is required, Adeza requests that the study be conducted post-approval."**

2. The requirement for a multi-center efficacy clinical trial

The Division stated in the Approvable Letter that "Further study is needed to provide confirmatory evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly or through a well-established surrogate, such as the rate of preterm birth prior to 35 and 32 weeks of gestation." To gain approval, the Division further stated that Adeza should "Submit a draft protocol and evidence of feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of 17HPC for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510. If a placebo-controlled trial is determined not to be feasible, provide alternative study design proposals."

Adeza believes that a confirmatory clinical trial should not be required even post-approval as outlined by The Division. However, if the "dispute resolution process resolution process determines that a clinical trial is required, Adeza requests that the draft protocol and evidence of feasibility be provided post-approval."

3. The requirement for a pre-approval protocol to evaluate the potential association of 17HPC with increased risk of second trimester miscarriages and stillbirth.

The Division stated in The Approvable Letter that "There are insufficient data to evaluate potential association of 17HPC with increase risk of early fetal loss (second trimester miscarriage and stillbirth)." Adeza should therefore "Provide a draft protocol to evaluate the potential association of 17HPC with the increase risk of second trimester miscarriages and stillbirth. This could be assessed as part of the confirmatory efficacy study referred in Item No. 1 (the efficacy trial) above."

In the dispute document **"Adeza believes that continued study of second trimester miscarriage and stillbirth rates associated with 17HPC is important. Adeza's expectation is that the protocol to evaluate the potential association of 17HPC with second trimester miscarriage and stillbirth be provided post approval. "**

2.0 <u>Background</u>

2.1 Clinical

Preterm birth, defined as delivery prior to 37 completed weeks of gestation, is a significant public health problem in the United States, with an increasing prevalence, currently affecting 12% of all births. Although there are a number of diagnostic tests proposed to identify women at risk for preterm labor and medications used off-label to treat preterm labor, there are no data indicating a benefit on neonatal morbidity or mortality from any of these interventions.

The National Institute of Child Health and Human Development (NICHD) initiated a multicenter, double blind, 2:1 randomized, vehicle-controlled clinical trial through its Maternal-Fetal Medicine Units (MFMU) Network in 1998 to evaluate the safety and efficacy of 17HPC in pregnant women with a history of spontaneous preterm birth. The initial trial (hereinafter referred to as 17P-IF-001) was terminated after about one year when the study drug was recalled by its manufacturer at the request of the FDA, due to violations of manufacturing processes that potentially could affect drug potency. At termination, only 150 of 500 planned women had been randomized, and only 86 women (57 of 17HPC treated women and 29 of vehicle treated women) had completed treatment.

The trial was started anew (referred to as 17P-CT-002) and enrolled 463 of a planned 500 women before

being terminated prematurely due to crossing the prespecified threshold for efficacy as determined by the Data Safety Monitoring Board. Results of the trial were published in the New England Journal of Medicine in June 2003. The American College of Obstetrics and Gynecology issued a Committee Opinion in November 2003 stating that "further studies are needed to evaluate the use of progesterone in patients with other high-risk obstetric factors, such as multiple gestations, short cervical length, or positive test results for cervicovaginal fetal fibronectin. When progesterone is used, it is important to restrict its use to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug." However, this opinion was viewed as supportive of the use of 17HPC for prevention of recurrent preterm birth, and use of compounded 17HPC has increased substantially since 2003.

17α-hydroxyprogesterone caproate is being compounded by pharmacists and is being used widely for prevention of preterm birth in women at high risk. Two mail surveys were sent to all board certified Maternal-Fetal Medicine (MFM) sub-specialists in the United States: one in December 2003 (response rate 42%) six months after the data submitted to this NDA was published in the New England Journal of Medicine and the other in March 2005 (response rate 47%). In 2005, 67% of the respondents used progesterone to prevent spontaneous preterm birth compared to 38% in 2003. Other progestogens were used in addition to 17HPC; these physicians also used progestogens in women with other risk factors in addition to a previous spontaneous preterm birth.

The drug substance (17HPC) was approved in 1956 under NDA 10-347 (with additional indications approved in 1972 under NDA 16-911) and marketed under the trade name Delalutin® for a variety of gynecological indications as well as for prevention of habitual, recurrent and threatened miscarriage. The sponsor discontinued marketing in the 1990's, and the NDAs were withdrawn "without prejudice" by the Agency in 2000. However, particularly since the publication of the 2003 New England Journal of Medicine article, 17HPC has been compounded by pharmacists and used in women at risk of preterm birth.

2.2 Regulatory

After data from Study 17P-CT-002 were published in the New England Journal of Medicine, Adeza met with DRUP to discuss the possibility of using these data as the basis for an NDA for 17HPC for the indication of prevention of preterm birth in pregnant women at high risk.

Study 17P-CT-002, however, had not been designed as a clinical trial to support marketing approval of 17HPC for prevention of preterm birth. The Division conveyed several recommendations and concerns to the Applicant during this and subsequent meetings. These included the following:

- The primary endpoint for Study 17P-CT-002 was a reduction in preterm births at < 37 weeks gestation. Although preterm birth is generally defined as a birth prior to 37 weeks gestation, the clinical significance of preterm birth is more pronounced at and prior to 32 weeks gestation. In the U.S., infants born after 32 weeks have very low mortality rates, and relatively low long-term morbidity. The Division asked Adeza to perform analyses of reduction of pre-term births at <35 and <32 weeks
- The primary endpoint of Study 17P-CT-002 (a reduction in preterm births at < 37 weeks gestation) is a surrogate for neonatal/infant morbidity and mortality. The Division indicated that its assessment of effectiveness also would also consider the demonstrated benefit of 17HPC on these latter outcomes, namely, overall survival of infants and a reduction in serious infant morbidities.
- There was the lack of follow-up data, beyond the period of initial hospital assessment, of children for whom their mother had received 17HPC for the prevention of preterm birth. The Division requested that the Applicant obtain follow-up developmental and safety data on children whose

mothers had participated in Study 17P-CT-002 through at least 2 years of age. This study would be called 17P-FU

- Normally, either 2 adequate and well-controlled studies or a single study with a robust and compelling outcome and strong supporting data would be required to support approval of a new drug product. There was a possibility that the data from Study 17P-CT-002 would not be sufficient to demonstrate that 17HPC is safe and effective for the prevention of preterm birth.

3.0 NDA 21-945

3.1 Contents of NDA

In support of their Application, Adeza submitted data from 2 active treatment clinical trials and a follow-up safety study: Study 17P-IF-001; Study 17P-CT-002; and Study 17P-FU. An overview of these studies is presented in Table 1. All of the studies were sponsored by the NICHD. Studies 17P-IF -001 and 17P-CT-002 were conducted in accordance with identical designs. Each was a double-blind, vehicle-controlled clinical trial, randomized 2:1 to 17HPC or vehicle, which enrolled pregnant women with a prior history of at least 1 spontaneous preterm birth. Treatment (a weekly injection of 250 mg 17HPC or vehicle) was initiated between 16^0 to 20^6 weeks gestation and continued through 36^6 weeks gestation or delivery, whichever occurred first.

Table 1 Clinical Studies of 17HPC in NDA 21-945

Protocol # / Status	Study Design	Study Population	Treatment Dose	Duration of Drug Treatment	Number of Subjects Enrolled	Number of Black/ Non-Black Subjects	Mean Age (Range)
17P-IF-001 Terminated Mar 1999[A]	Double-blind, Vehicle-controlled, Randomized 2:1 17OHP to Vehicle	Pregnant women with previous spontaneous preterm birth	250 mg 17OHP per week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 36^6 wks gestation or delivery	Total: 150 17OHP: 94 Vehicle: 56	Total: 95/55 17OHP: 54/40 Vehicle: 41/15	26.2 yr (17, 42)
17P-CT-002 Completed Aug 2002[B]	Double-blind, Vehicle-controlled, Randomized 2:1 17OHP to Vehicle	Pregnant women with previous spontaneous preterm birth	250 mg 17OHP per week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 36^6 wks gestation or delivery	Total: 463 17OHP: 310 Vehicle: 153	Total: 273/190 17OHP: 183/127 Vehicle: 90/63	26.2 yr (16, 43)
17P-FU Completed Nov 2005	Observational long-term safety follow-up for Study 17P-CT-002	Infants discharged live in Study 17P-CT-002	None	No study treatment was administered	Total: 278 17OHP: 194 Vehicle: 84	Total: 152/126 17OHP: 105/89 Vehicle: 47/37	47.4 mo (30, 64)

[A] Study 17P-IF-001 was terminated early by the Sponsor when the manufacturer recalled the study drug. The last subject visit was in August 1999. Of the 150 subjects, 104 subjects (65 randomized to 17HPC and 39 randomized to vehicle) had ended their treatment prior to the study termination either because they had completed treatment with study drugs completed study treatment to 36^6 weeks of gestation or delivery or had withdrawn prematurely for reasons other than recall of study drugs.

[B] An independent Data and Safety Monitoring Committee (DSMC) reviewed the study data after 400 subjects had completed the study. Based on that interim dataset, the primary endpoint, birth $<37^0$ weeks of gestation, was significantly reduced and the p-value was below the p-value specified in predefined stopping rules. The DSMC recommended that enrollment in the study be stopped, so that no new subjects would be assigned vehicle. By the time the study was stopped, 463 subjects had been enrolled, which was 92.5% of the proposed sample size of 500 subjects.

Source: Table 2, pg. 20 of primary Medical Review for NDA 21-945.

3.2 The Primary Study (17P-CT-002)

3.21 Efficacy

The primary objective of this study was to determine if treatment with 17HPC, initiated between 16^0 and 20^6 weeks gestation, compared with vehicle, reduced the risk of preterm birth (birth $<37^0$ weeks gestation) in women who had previously experienced a prior spontaneous preterm birth. The primary endpoint was the proportion of subjects in each treatment group who delivered at $< 37^0$ weeks gestational age.

Neonatal outcomes considered secondary efficacy measures included: birth weight; score reflecting condition of neonate (Apgar score); admission to the neonatal intensive care unit (NICU); infant hospital days; number of days of neonatal respiratory therapy; stillbirths; neonatal deaths; neonates with respiratory distress syndrome (RDS); intraventricular hemorrhage (IVH); bronchopulmonary dysplasia (BPD); necrotizing enterocolitis (NEC); early onset of neonatal sepsis; and seizures.

The percentages of preterm births, mean differences between treatment groups, and 95% confidence intervals (CIs) of the differences at < 37^0 weeks gestational age (protocol defined primary endpoint), and < 35^0, and < 32^0 weeks gestational age (secondary endpoints) are listed in Table 2. A lesser percentage of subjects in the 17HPC treatment group had preterm births at each of < 37^0, < 35^0, and < 32^0 weeks gestation.

Table 2 Proportion (95% Confidence Interval) of Subjects with Preterm Births at <37^0, <35^0, and <32^0 Weeks Gestational age

Gestation Age at Delivery	17HPC[A] (N=310)	Vehicle (N=153)	Mean Treatment Differences and 95% Confidence Interval [B]
	Percent of Preterm Births		
< 37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
< 35^0 weeks	21.3	30.7	-9.4% [-18.7%, -0.2%]
< 32^0 weeks	11.9	19.6	-7.7% [-16.1.%, -0.3%]

[A] Four 17HPC treated patients were lost-to-follow-up. They are counted as deliveries at their gestational ages at time of last contact (18.6, 22.0, 34.4, and 36.6 weeks).
[B] To preserve the overall Type I error rate of 0.05, the adjusted confidence intervals (equivalent to a 96.6% confidence interval) use the final p-value boundary of 0.0345.
Source: Table 3.1, FDA statistical review, October 19, 2006.

The differences in percentages of preterm births between the 17HPC and vehicle treatment groups at < 37, < 35, and < 32 weeks gestation each met the generally accepted criteria for statistical significance in Study 17P-CT-002. The reduction in preterm births < 37 weeks was statistically persuasive, even after adjusting for the 2 interim analyses. The reductions in preterm births of < 35 and < 32 weeks, although statistically significant, were not sufficiently persuasive for supporting approval of 17HPC based on the outcome of a single clinical trial.

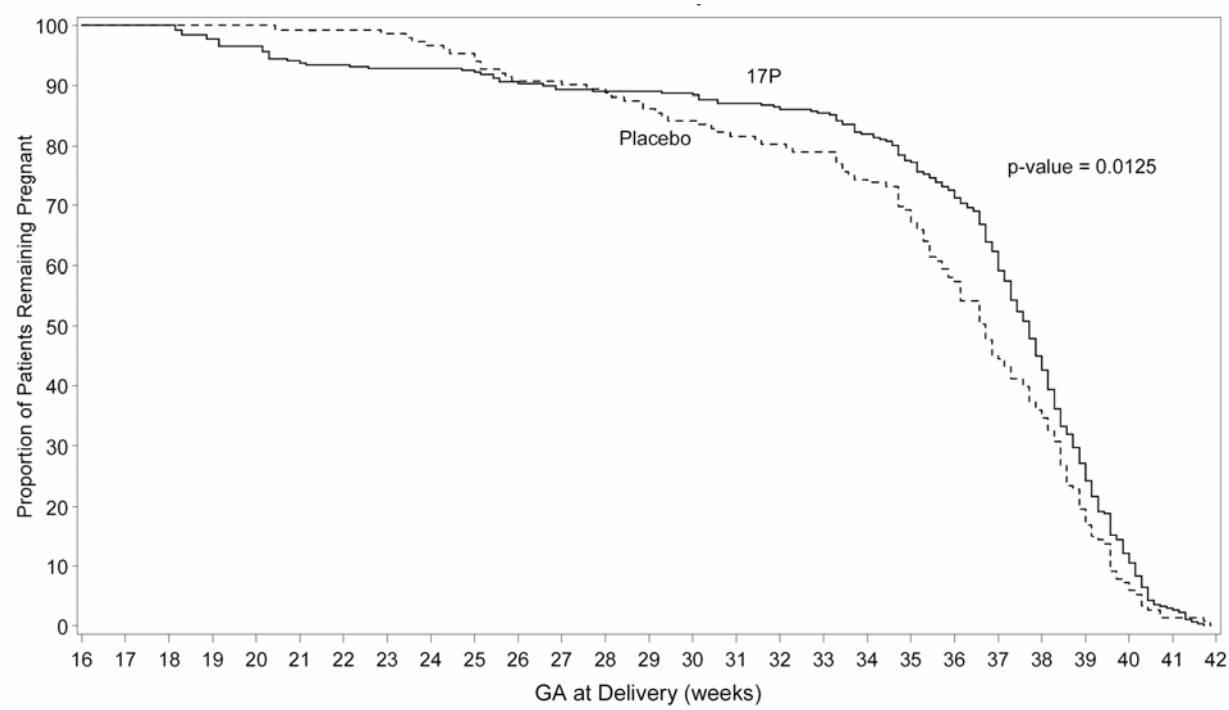
Results were consistent across all centers at < 37 and < 35 weeks. At < 32 weeks, however, there may be an interaction between center and treatment based on a greater difference between treatment groups (i.e., greater benefit of treatment with 17HPC) at the University of Alabama than was seen in the study as a whole or in all other centers combined. This suggests that the effect of 17HPC in prevention of preterm birth at < 32 weeks may not be consistent across centers.

The mean gestational age at delivery for subjects with available outcome data was one week greater in the 17HPC group (36.2 weeks vs. 35.2 weeks). The gestational ages at delivery ranged from 18.1 to 41.6 weeks. The median prolongation of pregnancy (defined as the time from randomization until delivery or date that the subject was last confirmed to be pregnant) was higher in the 17HPC group compared to the vehicle group (131 days vs. 125 days).

3.22 Early Fetal Loss

The Applicant provided a Kaplan Meier analysis of the time to delivery in the 2 treatment groups that showed a statistically significant difference in the shape of the curves by the log-rank test (see Figure 1).

Figure 1 Time to Delivery as a Function of Gestational Age, using Staggered Entry Based on the Gestational Age at Randomization (Study 17P-CT-002)



Source: Applicant's response to FDA's request dated 7/20/06.

The results of the log-rank test show that the difference in the shapes of the curves is statistically significant (p-value = 0.0125). Prior to approximately 25 weeks gestation, a numerically greater proportion of subjects randomized to the 17HPC group delivered at each gestational age; after 28 weeks gestation, a greater proportion of subjects randomized to the vehicle group delivered at each gestational age.

The increased proportion of delivered subjects in the 17HPC group, relative to the vehicle group, up to a gestational age of 25 weeks was due to 5 miscarriages (spontaneous abortions) in the 17HPC group and other early fetal losses (Table 3). Whether treatment with 17HPC contributed to these early pregnancy losses is not known.

3.23 Total Fetal and Neonatal Losses

The numbers of miscarriages, stillbirths, and neonatal deaths in each of the treatment groups are listed in (Table 3). Five of 306 subjects assigned to the 17HPC group experienced miscarriages. No subject in the vehicle group miscarried. The incidence of stillbirths also was slightly higher in the 17HPC group. Overall, 8 subjects had stillbirths: 6 subjects (2.0%) in the 17HPC group and 2 subjects (1.3%) in the vehicle group. The incidence of neonatal deaths was numerically twice as high in the vehicle group (5.9% vs. 2.6%), but the difference was not statistically significant. The overall incidence of fetal and neonatal mortality was similar in the 2 treatment groups (19 of 306 [6.2%] in the 17HPC group and 11 of 153 [7.2%] in the vehicle group).

Table 3 Miscarriages, Stillbirths, and Neonatal Deaths (Study 17P-CT-002)

Pregnancy Outcome	17HPC N=306 n (%) [A]	Vehicle N=153 n (%) [A]	Nominal P-value [B]
Miscarriages <20 weeks gestation	5 (2.4)[C]	0	0.17
Stillbirth	6 (2.0)	2 (1.3)	0.72
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.12
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.69**

[A] Percentages are based on number of enrolled subjects and not adjusted for time on drug.
[B] No adjustment for multiple comparisons.
[C] Percentage adjusted for the number of at risk subjects (n=211) enrolled at < 20 weeks gestation.
Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

The Kaplan-Meier analysis of time to delivery demonstrated a statistically significant difference between "survival" curves for the two treatment groups, reflecting a prolongation of pregnancy in the 17HPC group from about 28 weeks of gestation on, but an increased risk of preterm delivery from the time of enrollment to about 25 weeks of gestation.

Although there was a numerically lower rate of neonatal mortality in the 17HPC group, the increased rate of early fetal loss in this group led to an overall finding of no difference in fetal/neonatal mortality across the 2 treatment groups.

3.24 Other Neonatal Outcomes

Additional endpoints evaluated neonatal outcomes, including the proportions with birth weight of < 2500 and < 1500 g. The 17HPC group had a statistically significantly lower percent of < 2500 g infants (27% compared to 41% of vehicle-exposed neonates). The trend toward a lower proportion of < 1500 g infants (8.6% in the 17HPC group vs. 13.9% in the vehicle group) was not statistically significant. Mean birth weight was numerically, but not statistically greater in the 17HPC treatment group. There were no differences in mean 1 and 5 minute Apgar scores between offspring of 17HPC and vehicle-treated women. Neonatal intensive care unit (NICU) admission, NICU stay, and hospital stay also were compared; only NICU admission differed significantly between groups, with 28% of 17HPC exposed infants admitted vs. 36% of vehicle-exposed infants.

Other secondary outcome measures did not show a consistent pattern of benefit for treatment with 17HPC. In particular, measures of neonatal outcome generally did not differ between treatment groups; however, the study was not powered to detect such differences.

3.25 General Safety

There were no important differences in adverse events between treatment groups or significant signals regarding Maternal or Fetal/Child safety other than that discussed in section 3.32 (early fetal loss).

3.3 Supportive Study 17P-IF-001

Study 17P-IF-001 might be considered a supportive efficacy study, although of limited value due to early termination and questions about study drug potency. This trial was of the same design and used the same inclusion and exclusion criteria as Study 17P-CT-002.

3.31 Efficacy

There is no evidence of a treatment effect for 17HPC in this study, even in the population subset unaffected by study drug recall. However, questions about the drug potency limit the reliability of this finding.

3.32 Safety

The combined fetal/neonatal death rate in the ITT population did not differ statistically between treatment arms (4.4% in the 17HPC arm and 5.9% in the vehicle arm).

3.4 Supportive Study 17P-FU

Infants born to women enrolled in Study 17P-CT-002, who survived to be discharged from the nursery, were eligible for participation in the follow-up safety study (Study 17P-FU).

The study collected data with a validated child development instrument (the Ages and Stages Questionnaire [ASQ]), a Survey Questionnaire concerning the health and development of the child, and a physical examination. All children were at least 2 years of age at the time of the follow-up assessments. The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received weekly intramuscular injections of 17HPC compared with vehicle in Study 17P-CT-002. Two hundred seventy eight (278) children were enrolled: 194 from the 17HPC group and 84 from the vehicle group of Study 17P-CT-002.

The ASQ was completed for 275 children, 193 from the 17HPC group and 82 from the vehicle group. The age of the children at the time of completion of the ASQ ranged from 30 to 64 months; mean age at time of completion did not differ between the 17HPC and vehicle groups (47.2 vs. 48.0 months). The ASQ responses were categorized to assess communication, gross motor, fine motor, problem solving, and personal-social development. Using threshold scores (cutoffs) for normal development, the percentages of children who had scores below the cutoffs for the 5 areas of development were determined.

The percentage of children who scored below the cutoff in at least one developmental domain was comparable in the 2 treatment groups (27.5% in the 17HPC group and 28.0% in the vehicle group. The proportions of children below the cutoff in each developmental domain also were similar across treatment groups.

Thirteen (6.7%) of the 193 children in the 17HPC group and 8 (9.8%) of the 82 children in the vehicle group had an ASQ score below cutoff for at least one developmental area and a reported diagnosis of developmental delay (either in a specific area or overall). Based on this small number of children and the other assessments, there is no suggestion of any adverse effects on postnatal development in the children whose mothers had been treated with 17HPC during their pregnancy.

3.5 Advisory Committee meeting

The Advisory Committee for Reproductive Health Drugs (ACRHD) met on August 29, 2006 to discuss this Application. The Advisory Committee was asked to vote on several issues that included the following.

Issue 1. *Is a reduction in preterm birth prior to 37, 35, or 32 weeks gestation an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity?*

- The Committee stated clearly that a reduction in preterm birth < 37 weeks was not an adequate surrogate (yes=5, no=16) but that reductions in preterm birth < 35 weeks (yes=13, no=8) and < 32 weeks (yes=20, n=1) were adequate surrogates.

Issue 2. *Do the data provide substantial evidence that (a) 17HPC prevents preterm birth earlier than either 35 or 32 weeks gestation and (b) 17HPC reduces fetal and neonatal mortality or morbidity?*

- The Committee (by a small majority) indicated that the data provided substantial evidence that 17HPC (a) prevents preterm birth < 35 weeks (yes=12, no=9) but not < 32 weeks (yes=7, no=14). The Committee also clearly stated that the data did not provide substantial evidence that 17HPC reduces fetal and neonatal mortality or morbidity (yes=2, no=19).

Issue 3. *Is further study needed to evaluate the potential association of 17HPC with increased risk of second trimester miscarriage and stillbirth and if so, should this information be obtained prior to approval for marketing or post approval?*

- The Committee was unanimous in its recommendation that further study was needed (yes=21, no=0) but a majority felt that this information could be obtained post approval (pre-approval=8, post approval=13).

Issue 4. *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 17HPC without the need for additional pre-approval safety data?*

- A majority of the Committee voted that the existing safety data were sufficient to support marketing approval of 17HPC without the need for additional pre-approval safety data (yes=13, no=8).

Issue 5. *Would the Committee recommend post approval clinical trial(s) to investigate further safety or effectiveness?*

- The Committee was unanimous in its recommendation that post approval clinical trial(s) to investigate further safety and/or effectiveness be conducted (yes=21. no=0).

Overall a majority of the Committee members indirectly expressed support for approval based on the following 3 votes:

1. Thirteen of the 21 members voted that a reduction in preterm birth < 35 weeks was an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity;
2. Twelve of the 21 members voted that the Applicant's data provided substantial evidence that 17HPC prevents preterm birth < 35 weeks gestation; and
3. Thirteen of the 21 members voted that the existing safety data were sufficient to support marketing approval of 17HPC without the need for additional pre-approval safety data

The committee was unanimous in recommending that further study was needed to evaluate the potential association of 17HPC with increased risk of second trimester miscarriage and stillbirth, but a majority (13 of 21 members) stated that this information could be obtained post approval.

These recommendations would support approval under the sub-part H regulation because approval would be based on a surrogate of infant morbidity and mortality.

3.6 Toxicology Issues

Meetings were held between Adeza Biomedical and DRUP on 30 January 2004, 5 April 2004 and 16 July 2004 under IND 68,108 to discuss the overall drug development program leading to a submission of a 505(b)(2) NDA. A Pre-NDA meeting with the applicant was held on 27 June 2005. At these meetings Adeza was told that no additional nonclinical studies would be needed to file a NDA. At that time, it was thought that there was sufficient clinical and nonclinical safety data to support the safety of 17-HPC.

After a review of the published nonclinical data the Pharmacolgy/Toxicology (P/T) Team was found that there were significant deficiencies in the scope and quality of the reported nonclinical studies. Most of the nonclinical studies were old and did not comply with either Good Laboratory Practices or conform to current CDER and ICH guidances. The primary deficiencies in the nonclinical studies included insufficient

numbers of animals, use of unconventional species, lack of any PK/ADME data, correlation between gestational timing of exposures and pregnancy outcome, and lack of developmental studies in offspring exposed in utero.

The toxicology team was particularly concerned about data in several articles by Pushpalatha culminating in an article published in July 2005. In this study 17HHPC was administered to pregnant rats early in pregnancy. The effect of gestational exposure to 17HPC on fertility was assessed by breeding F1 male rats with control females as well as analyzing sperm quality and quantity in the F1 males. The number of implantation sites and viable fetuses was significantly reduced in females mated with F1 males that were exposed to 17HPC during embryonic development. The decrease in sperm function was associated with a decrease in sperm motility, sperm viability and sperm count in the F1 rats. The conclusion was that in utero exposure to 17HPC affects fertility in male rats. The P/T team did not raise these concerns until after the Advisory Committee meeting was held.

The Pushpalatha studies were not performed according to GLP and did not closely mimic the clinical administration of 17HPC as proposed by Adeza. For these reasons, The P/T team did not believe that data from the Pushpalatha studies would be particularly informative to patients or prescribers. The team, therefore, did not believe that data from these studies were appropriate for product labeling.

The P/T team concluded that there was insufficient nonclinical data on which to base the safety of 17-HPC, especially in regards to long-term effects in offspring exposed in utero. The team recommended that a thorough reproductive and developmental study be performed in accordance with ICH S5A "Guideline for Industry: Detection of toxicity to Reproduction for Medicinal Products". A multigenerational study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including learning, behavior and reproductive function, in offspring exposed in utero.

3.7 Conclusions Regarding Safety and Efficacy

3.71 Efficacy

The differences in percentages of preterm births between the 17HPC and vehicle treatment groups at < 37, < 35, and < 32 weeks gestation in Study 17P-CT-002 each met the generally accepted criteria for statistical significance. The reduction in preterm births < 37 weeks was statistically persuasive, even after adjusting for the 2 interim analyses. The reductions in preterm births of < 35 and < 32 weeks, although statistically significant by generally accepted criteria, were less persuasive.

The clinical and statistical reviewers of this Application raised questions as to whether the evidence of efficacy from this single Phase 3 study is adequate and sufficiently convincing to support approval. The clinical trial data did not provide evidence of a statistically significant effect on a composite endpoint of major neonatal morbidities and neonatal mortality. However, a majority of the members of the ACRHD believed that preventing preterm birth at < 35 and < 32 weeks of gestation represents an adequate surrogate for a reduction in neonatal morbidity and mortality. A majority of committee members also thought that there was a significant reduction in preterm births < 35 weeks gestation in Study 17-CT-002. However, the level of statistical significance for the treatment effect at <35 weeks and <32 weeks gestation does not meet the level of statistical significance generally expected by the FDA to support approval of a drug product based on the findings from a single clinical trial.

3.72 Safety

The clinical finding of concern was an increase in early pregnancy loss in the 17HPC treated subjects. There was a trend toward an increase in second trimester miscarriage rate (pregnancy loss prior to 20 weeks of gestation) and a suggestion of an increase in stillbirth rate (death of the fetus prior to or during delivery) in the 17HPC group. These findings were presented to the members of the ACRHD. The recommendation of the majority of the members was that this observation required further investigation, but the investigation could be conducted post approval. A majority of the committee members also voted that no additional clinical safety data were required prior to approval.

Since this drug was on the market for many years and is currently being used in clinical practice (obtained from compounding pharmacies), a post-marketing safety review was requested form the Office Of Safety and Epidemiology The consult stated that no conclusions can be made at this point in time from the limited number of reports in AERS for 17α-hydroxyprogesterone caproate.

4.0 Conclusions Regarding the Dispute from the Office of Drug Evaluation III

On April 26th, 2006, Adeza submitted NDA 21-945 to the Division of Reproductive and Urologic Products (DRUP) for 17HPC with the proposed induction of "Prevention of preterm birth in women with a history of at least one spontaneous preterm birth." The Division granted a priority review and held an Advisory Committee meeting on August 29th, 2006. On October 26th, 2006, DRUP wrote an Approvable Letter to Adeza communicating deficiencies and information required to address said defiencies before approval could be granted. A post-action meeting with the sponsor was held on November 9th, 2006.

On March 16th, 2006, Adeza submitted a Formal Dispute Resolution Request to the Office of Drug Evaluation III regarding three specific scientific requirements stipulated by the Division in the Approvable Letter.

In preparation for addressing Adeza's request for dispute resolution, I reviewed the package, submitted by you dated March 14th, 2007, documents generated by the review team in support of the Approvable Action, documents related to the administrative record, relevant primary material and literature. I further interviewed members of the review team on specific issues, as necessary for my complete understanding of the issues.

Adeza is disputing three requirements of approval as communicated by DRUP in the Approvable Letter of October 20th, 2006; I will address each of them separately.

#1. The requirement for a GLP compliant multi-generational reproductive toxicity study in animals.

The Division stated in the Approvable Letter "that at the time of a Complete Response submission to this approvable letter, provide at a minimum, an unedited interim final report of the requested {reproductive toxicity} study." Adeza believes that "During initial discussions with the Division regarding preclinical safety data, the Division stated that existing published data would be sufficient to support the NDA…consequently Adeza did not initiate any preclinical studies." In addition, Adeza believes that "substantive and relevant toxicology studies were provided to the NDA and subsequent amendments to the NDA." Therefore, Adeza believes that this reproductive toxicology study is not required for approval. However, "if the dispute resolution process determines that a rodent study is required, Adeza requests that the study be conducted post-approval."

Adeza expressed two issues of concern under Dispute # 1. The first is that on multiple occasions, Adeza supplied all relevant toxicological material to DRUP even throughout the NDA review period. Adeza believes that on all these occasions, the Division explicitly expressed to Adeza that the information submitted would be sufficient to fulfill the toxicology requirements of the NDA. Adeza believes that no concerns were raised by the Division even as late as the Advisory Committee meeting regarding toxicology.

Adeza believes that it was only during communications in October and November of 2006 that the Division addressed concerns regarding Adeza's toxicology package, specifically the need for a GLP multi-generational reproductive toxicology study in rodents that would now be a pre-approval requirement.

After review of the relevant documents, I agree that Adeza was informed very late in the review process that a new pre-approval toxicology study would be required. I agree with Adeza that DRUP had informed Adeza on multiple occasions during the development of the NDA package that no additional toxicology material would be necessary. As flawed as the communications by DRUP may have been, however, this process in itself cannot negate the need for a toxicology study if the study's presence is required for assurance of safe use and appropriate labeling of the product.

The second issue expressed by Adeza is that, in fact, 17HPC can be administered safely and it can be appropriately labeled by evaluation of the submitted published toxicology studies. The FDA toxicologists have general concerns that "after a review of the published nonclinical data it was found that there were significant deficiencies in the scope and quality of the reported nonclinical studies. Most of the nonclinical studies were old and did not comply with either Good Laboratory Practices or conform to current CDER and ICH guidances."

A particular concern of the FDA toxicologists appears to be information generated by the series of articles by Pushpalatha culminating in a paper published in 2005. In this study, 17HPC was administered to pregnant rats early in gestation. The effect of gestational exposure to 17HPC on fertility was assessed by breeding F1 male rats with control females as well as analyzing sperm quality and quantity in the F1 males. The number of implantation sites and viable fetuses was significantly reduced in females mated with F1 males that were exposed to 17HPC during embryonic development. The decrease in sperm function was associated with a decrease in sperm motility, sperm viability and sperm count in the F1 rats. The conclusion was that in utero exposure to 17HPC affects fertility in male rats.

I agree with the Division, that the GLP multi-generational study will provide important information to patients and providers regarding the potential risks of 17HPC. I further agree with the Division that the preliminary results of this study, as described in the Approvable Letter, should be available pre-approval. I believe that the Pushpalatha studies have significance flaws and are not appropriate for labeling because the results may misinform patients and prescribers regarding the risks of 17HPC. I believe that a multi-generational reproductive toxicology study performed under GLP that closely mimics the clinical administration of 17HPC would be best suited for labeling and informing patients and prescribers.

Therefore, with regard to Dispute issue #1, I wholly concur with DRUP's position as communicated in the Approvable Letter of October 26th, 2006.

#2 The requirement for a multi-center efficacy clinical trial

The Division stated in the Approvable Letter that "Further study is needed to provide confirmatory evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly or through a well-established surrogate, such as the rate of preterm birth prior to 35 and 32 weeks of gestation." To gain approval, the Division further stated that Adeza should "Submit a draft protocol and evidence of feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of 17HPC for the prevention of recurrent preterm birth, as consistent with Subpart H 21 CFR 314.510. If a placebo-controlled trial is determined not to be feasible, provide alternative study design proposals."

Adeza believes that a confirmatory clinical trial should not be required even post-approval as outlined by The Division. However, if the "dispute resolution process determines that a clinical trial is required, Adeza requests that the draft protocol and evidence of feasibility be provided post-approval."

When the Advisory Committee was asked, "Would the Committee recommend post approval clinical trial(s) to investigate further safety or effectiveness?" , the Committee was unanimous in its recommendation that post approval clinical trial(s) to investigate further safety and/or effectiveness be conducted (yes=21, no=0).

FDA's clinical and statistical reviewers for this Application have raised questions as to whether the evidence of efficacy from this single Phase 3 study is adequate and sufficiently convincing to support approval. The clinical trial data did not provide evidence of a statistically significant effect on a composite endpoint of major neonatal morbidities and neonatal mortality. However, a majority of the members of the Advisory Committee believed that preventing preterm birth at < 35 and < 32 weeks of gestation represents an adequate surrogate for a reduction in neonatal morbidity and mortality. A majority of committee members also thought that there was a significant reduction in preterm births < 35 weeks gestation in Study 17-CT-002. However, the level of statistical significance for the treatment effect at <35 weeks and <32 weeks gestation did not meet the level of statistical significance generally expected by the FDA to support approval of a drug product based on the findings from a single clinical trial.

Although the Applicant has demonstrated efficacy of 17HPC for reducing the risk of preterm birth at gestational ages (surrogate measures), that correlates with increased neonatal morbidity and mortality in a single trial, the data are not sufficiently robust or compelling to support approval without binding commitments on the part of Adeza to perform an additional clinical study as described in the Approvable Letter. I believe that DRUP exhibited appropriate prudence by asking Adeza to submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify the observed clinical benefit of 17HPC for the prevention of recurrent preterm birth, consistent with Subpart H 21 CFR 314.510. I further concur with DRUP's statement that if a vehicle-controlled trial is determined not to be feasible, Adeza should provide alternative study design proposals. I believe that DRUP's pre-approval requirements and their approach of using Sub Part H 21 CFR 314.510 to assure performance of the described post approval clinical trial(s) are consistent with the public health needs as well as the advice of the Advisory Committee on Reproductive Health.

Therefore, with regard to Dispute issue #2, I wholly concur with DRUP's position as communicated in the Approvable Letter of October 26th, 2006.

#**3. The requirement for a pre-approval protocol to evaluate the potential association of 17HPC with increased risk of second trimester miscarriages and stillbirth.**

The Division stated in the Approvable Letter that "There are insufficient data to evaluate the potential association of 17HPC with an increased (check exact wording) risk of early fetal loss (second trimester miscarriage and stillbirth)." Adeza should therefore "Provide a draft protocol to evaluate the potential association of 17HPC with the increased risk of second trimester miscarriages and stillbirth. This could be assessed as part of the confirmatory efficacy study referred in Item No. 1 (i.e., the efficacy trial described in Dispute issue #2)."

In Dispute issue #3 "Adeza believes that continued study of second trimester miscarriage and stillbirth rates associated with 17HPC is important. Adeza's expectation is that the protocol to evaluate the potential association of 17HPC with second trimester miscarriage and stillbirth be provided post approval.

In general, there were no worrisome safety findings from Study 17P-CT-002, supportive Study 17P-IF-001, and follow-up Study 17P-FU that would preclude approval of 17HPC for the proposed indication. A particular finding of concern, however, was an increase in early pregnancy loss in the 17HPC treated

subjects. There was a trend toward an increase in second trimester miscarriage rate (pregnancy loss prior to 20 weeks of gestation) and a suggestion of an increase in stillbirth rate (death of the fetus prior to or during delivery) in the 17HPC group. These findings were presented to the members of the Advisory Committee. The recommendation of the majority of the members was that this observation required further investigation, but the investigation could be conducted post approval. A majority of the committee members also voted that no additional clinical safety data were required prior to approval.

The Committee was asked during the August 29, 2006 meeting "Is further study needed to evaluate the potential association of 17HPC with increased risk of second trimester miscarriage and stillbirth and if so, should this information be obtained prior to approval for marketing or post approval?" The Committee was unanimous in its recommendation that further study was needed (yes=21, no=0) but a majority felt that this information could be obtained post approval (pre-approval=8, post approval=13).

I believe that DRUP exhibited appropriate prudence by requiring submission of a "draft protocol to evaluate the association of 17HPC with second trimester miscarriages and stillbirths". I agree that this safety concern could be studied as part of the efficacy trial described in Dispute issue #2. I further believe that, as with Dispute issue #2, that DRUP's pre-approval requirements and their approach of using Sub Part H 21 CFR 314.510 to assure performance of the described post approval clinical trialare consistent with the public health needs as well as the advice of the Advisory Committee on Reproductive Health.

Therefore, with regard to Dispute issue #3, I wholly concur with DRUP's position as communicated in the Approvable Letter of October 26th, 2006.

5.0Regulatory Action for Formal Dispute Resolution

The following statements should be placed in a regulatory letter and conveyed to Adeza:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gestiva™ (17 α-hydroxyprogesterone caproate injection).

Your March 14, 2007, request for formal dispute resolution, received on March 16, 2007, concerned the October 20, 2006 approvable letter for the Gestiva™ NDA in which several deficiencies were stated including the need for an additional study to confirm evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality, data to evaluate a potential association of 17 α-hydroxyprogesterone caproate (17HPC) with increased risk of early fetal loss (second trimester miscarriage and stillbirth) and the need for, at minimum, preliminary data from multi-generational reproductive toxicology studies pre-approval. Your request for dispute resolution states your position that the above requirements exceed the recommendations of the Reproductive Health Drugs Advisory Committee (RHDAC) discussed at the August 29, 2006 meeting of this committee.

I have reviewed your appeal and conclude that the requirements stated in the October 20, 2006 approvable letter are appropriate. The rationale for this conclusion is detailed in the following responses to the points made in your appeal:

1. The requirement for a multi-generation reproductive toxicology study in rodents.

Your request stated two issues of concern relating to toxicological information required for approval. The first was that during initial and subsequent communications with the Division of Reproductive and Urologic Products (DRUP) regarding preclinical safety data, Adeza believed that the division explicitly indicated that the scope of information proposed for inclusion in NDA 21-945 was sufficient and that notification that a multi-generational reproductive toxicology study in rodents would be a pre-approval requirement was conveyed late (October and November 2006) in the review of the NDA. You asserted in your request that "…substantive and relevant toxicology studies were provided to the NDA and subsequent amendments to the NDA." and that the reproductive toxicology study is not required for approval. However, you also propose that if such a study is determined to be necessary, it should be permitted to be conducted post-approval. Your second concern is that, in fact, Gestiva™ can be administered safely and be appropriately labeled based on evaluation of the submitted published toxicology studies.

After review of the relevant documents, I agree that Adeza was informed late in the review process that a new pre-approval toxicology study would be required. I also acknowledge that DRUP communicated to Adeza on multiple occasions during the development of the NDA application that no toxicology data beyond what was proposed for the application appeared necessary. As flawed as the communications may have been, however, this process in itself cannot negate the need for full information necessary to assure safe use and appropriate labeling of Gestiva™. In addition, after review of the submitted information, the FDA toxicologists determined that there were significant deficiencies in the scope and quality of the reported nonclinical studies. Most of the nonclinical studies did not comply with either Good Laboratory Practices (GLP) or conform to current CDER and ICH guidances. Although exact conformance to guidances is not required, they do convey information on how to address data that is needed to support safety and efficacy. A particular concern of the FDA toxicologists focused on data found in a series of articles by Pushpalatha that culminated in a paper published in 2005. In this study, 17HPC was administered to pregnant rats early in gestation. The effect of gestational exposure to 17HPC on fertility was assessed by breeding F1 male rats with control females as well as analyzing sperm quality and quantity in the F1 males. The number of implantation sites and viable fetuses was significantly reduced in females mated with F1 males that were exposed to 17HPC during embryonic development. The decrease in sperm function was associated with a decrease in sperm motility, sperm viability and sperm count in the F1 rats. The conclusion was that in utero exposure to 17HPC affects fertility in male rats.

I agree with DRUP that a multi-generational study in rats conducted according to GLPs will provide important information that is needed in labeling to properly inform healthcare practitioners and patients regarding the potential risks of Gestiva™. I further agree with DRUP that the preliminary results of this study, as described in the approvable letter, should be available pre-approval. The Pushpalatha studies have significant flaws and are not useful for labeling because the results may misinform patients and prescribers regarding the risks of Gestiva™. A multi-generational reproductive toxicology study in rats performed according to GLPs that closely mimics the clinical administration of Gestiva™ will be best suited for generating the information needed for labeling.

2. The requirement for a confirmatory multi-center efficacy clinical trial.

The approvable letter suggested that the requirement for a confirmatory multi-center efficacy trial could be conducted post-approval under the regulations for accelerated approval at 21 CFR 314.510. Such a trial

would evaluate evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly or through a well-established surrogate. DRUP also specified in the letter that the draft protocol for and evidence of feasibility of conducting this trial be included in any response to the approvable action. In addition, if Adeza determined that a placebo-controlled trial would not be feasible, an alternative study design should be submitted. Your dispute resolution request states that a confirmatory clinical trial should not be required even post-approval as outlined by DRUP. You also request that if it is determined that a clinical trial is required, the draft protocol and evidence of feasibility be permitted to be provided post-approval. You also point out that the Advisory Committee recommended that a clinical trial to investigate further safety and/or effectiveness could be conducted post-approval.

The data generated by the single clinical trial provided in the NDA did not provide evidence of a statistically significant effect on a composite endpoint of major neonatal morbidities and mortality. However, a majority of the members of the Advisory Committee believed that preventing preterm birth at less than 32 and less than 35 weeks of gestation does represent an adequate surrogate for a reduction in neonatal morbidity and mortality. A majority of committee members also thought that there was a significant reduction in preterm births at less than 35 weeks gestation in Study 17-CT-002. However, the level of statistical significance for the treatment effect at less than 32 weeks and less than 35 weeks gestation did not meet the level of statistical significance generally accepted by FDA to support approval of a drug product based on the findings from a single clinical trial.

I have concluded that although Adeza has demonstrated efficacy of Gestiva™ for reducing the risk of preterm birth at gestational ages (surrogate measures) that correlate with increased neonatal morbidity and mortality in a single trial, the data are not sufficiently robust or compelling to support approval without the requirement for conduct of an additional clinical study(ies) as described in the approvable letter. I have also concluded that the accelerated approval regulations at 21 CFR 314.510 are applicable in this situation. DRUP exhibited appropriate prudence by requesting submission of a draft protocol and evidence of feasibility for a study to verify the observed clinical benefit of Gestiva™ for the prevention of recurrent preterm birth. Therefore, I concur with DRUP's position as communicated in the approvable letter.

3. The requirement for a pre-approval protocol to evaluate the potential association of 17HPC with increased risk of second trimester miscarriage and still birth.

DRUP recommended in the approvable letter, that the risk of second trimester miscarriages and stillbirth could be assessed as part of the confirmatory efficacy study described above. In addition, the division specified that the draft protocol be included in Adeza's response to the approvable action, again as stated above. Your dispute resolution request acknowledged that continued study of second trimester miscarriages and still birth rates associated with 17HPC is important but reiterated the request that the draft protocol be provided post-approval.

An increase in early pregnancy loss in the Gestiva™ treated subjects was a particular concern. There was a trend towards an increase in second trimester miscarriage rate (pregnancy loss prior to 20 weeks of gestation) and a suggestion of an increase in stillbirth rate (death of the fetus prior to or during delivery) in the Gestiva™ group. These findings were presented at the RHUAC meeting and the recommendation of the majority of the members was that this observation required further investigation (yes=21, no=0), but

that the investigation could be conducted post approval (pre-approval=8, post-approval=13). A majority of the committee members also voted that no additional clinical safety data were required prior to approval.

DRUP again exhibited appropriate prudence in requiring submission of a draft protocol to evaluate the association of Gestiva™ with second trimester miscarriages and stillbirths. I agree that this safety concern could be studied as part of the efficacy trial described above and that the accelerated approval regulations at 21 CFR 314.510 are applicable in this situation. Therefore, I concur with DRUP's position as communicated in the approvable letter.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daniel A. Shames
4/12/2007 06:08:52 PM
MEDICAL OFFICER
Response to Dispute

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)
DIVISION DIRECTOR MEMORANDUM

NDA	NDA 21-945
Type of Application	Original Application
Applicant	Adeza Biomedical Sunnyvale, CA 94089
Proprietary Drug Name	Gestiva (proposed)
Established Drug Name	17 α-hydroxyprogesterone caproate injectable
Drug Class	Progestogen
Indication	Prevention of preterm birth in women with a history of at least one spontaneous preterm birth
Route of administration	Intramuscular
Dosage Form	Injectable
Dosage Strength	17 α-hydroxyprogesterone caproate (250 mg/mL) in castor oil with 46% benzyl benzoate and 2% benzyl alcohol
Dosing Regimen	Once weekly injections of 17 α-hydroxyprogesterone caproate (250 mg in one mL) starting between 16 weeks 0 days and 20 weeks 6 days gestation to 37 weeks gestation or until birth
CDER Receipt Date	April 20, 2006
PDUFA Goal Date	October 20, 2006 (priority review)
Date of Memorandum	October 20, 2006
Reviewer	Scott E. Monroe, MD Acting Division Director, DRUP

1. RECOMMENDATIONS

1.1 Recommendation regarding Approvability

I concur with the recommendations of the primary Medical Reviewer (Barbara Wesley, MD) and the clinical Team Leader (Lisa Soule, MD) that NDA 21-945 (17 α-hydroxyprogesterone caproate [17OHP-C]) is approvable for the proposed indication of "prevention of preterm birth in women with a history of at least one spontaneous preterm birth." Eventual approval of 17OHP-C for the proposed indication is contingent upon the Applicant's satisfactorily addressing and resolving the clinical, toxicology, and (chemistry, manufacturing, and controls [CMC]) issues described in Sections 1.2 and 1.3 of this Memorandum and the Approvable Letter of October 20, 2006.

1.2 Basis for Recommendation regarding Approvability and Information Needed to Address Deficiencies

1.2.1 Clinical Issues

Deficiencies

1. The current submission provides data from a single Phase 3 multicenter, randomized, vehicle-controlled trial to support the efficacy of 17 α-hydroxyprogesterone caproate (17OHP-C) for the prevention of recurrent preterm birth. The FDA's Guidance Document entitled *Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)* discusses the usual requirement that effectiveness of a drug product be established by "two adequate and well-controlled studies, each convincing on its own." Although there are situations where efficacy data from a single clinical trial are sufficient to support approval, the clinical and statistical reviewers have raised questions as to whether the evidence of efficacy from the single Phase 3 study is adequate and sufficiently convincing. In this submission, the Applicant is seeking approval for 17OHP-C based on a demonstrated reduction in the incidence of preterm births, a surrogate endpoint for neonatal/infant morbidity and mortality. Although preterm birth is defined as a birth prior to 37 weeks gestation, the morbidity and mortality associated with preterm birth is more pronounced at < 35 and < 32 weeks gestation. In the U.S., infants born after 32 weeks gestation have very low mortality rates, and relatively low long-term morbidity. The Applicant's single Phase 3 clinical trial demonstrated a statistically strong reduction in the incidence of preterm births prior to 37 weeks gestational age, the protocol defined primary endpoint. However, the reduction in preterm births at earlier gestational ages (i.e., <35 weeks and < 32 weeks), although statistically significant, did not meet the level of statistical significance generally expected to support approval of a drug product based on the findings from a single clinical trial.
2. The findings of the clinical trial also raised concern about an increase in early pregnancy loss in the 17OHP-C treated subjects. There was a trend toward an increase in the late second trimester miscarriage rate (pregnancy loss prior to 20 weeks of gestation) and a suggestion of an increase in the stillbirth rate (death of the fetus prior to or during delivery) in the 17OHP-C group compared to the vehicle group.

Information Needed to Address the Deficiencies (to be provided prior to possible Approval)

1. The Applicant should submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of 17OHP-C for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510. If a placebo-controlled trial is determined not to be feasible, the Applicant should provide alternative study design proposals.
2. The Applicant should provide a draft protocol to evaluate the potential association of 17OHP-C treatment with increased risk of second trimester miscarriage and stillbirth. This could be assessed as a part of the confirmatory efficacy study referred to in Item No. 1.

1.2.2 Toxicology

Deficiency

The Supervisory Pharmacologist, Lynnda Reid, PhD, stated in her review, signed October 5, 2006, that from a Pharmacology/Toxicology standpoint the NDA is approvable. She also stated that there are insufficient nonclinical data on which to base the safety of 17OHP-C, especially in regards to long-term effects in offspring exposed *in utero*. She recommended that a thorough reproductive and developmental study be performed in accordance with ICH S5A "Guideline for Industry: Detection of Toxicity to Reproduction for Medicinal Products."

Information Needed to Address the Deficiency (to be provided prior to possible Approval)

The Applicant needs to conduct a GLP-compliant, multigenerational reproductive toxicology study evaluating all stages of pregnancy during which dosing will be administered in humans. The study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including learning, behavior, and reproductive function in offspring exposed *in utero*. At the time of a Complete Response to the Approvable Letter, the Applicant needs to provide, at a minimum, an unaudited interim final report of the requested study. Both the clinical and toxicology reviewers believe that the results from this study be need to be reviewed by the Division prior to possible approval of 17OHP-C for the proposed indication.

1.2.3 Chemistry, Manufacturing and Controls (CMC)

Deficiencies

The following deficiencies were identified by the primary Chemistry Reviewer, Monica Cooper, PhD., in her review dated September 22, 2006:

1. Significant degradation was observed for the light-stressed drug product sample with respect to content (assay) during the HPLC method validation studies. Thus, the drug product appears to be photosensitive; however, the resulting photo degradation products were not detectable by the Applicant's HPLC method.
2. The Applicant has not demonstrated that the proposed secondary packaging provides adequate light protection for the drug product because the results from the photostability study showed decreases in content (assay) from that of the control (wrapped in foil) in both the Stage 1 (fully exposed to light) and Stage 2 (enclosed in a chipboard box) samples.
3. The proposed expiration date of 24 months for the drug product is not acceptable based on the stability data included in the Application to date.

Information Needed to Address the Deficiencies (to be provided prior to possible Approval)

1. The Applicant should develop a supporting method that can adequately detect and quantitate the potential photo degradation products. The drug product specifications should include limits for any potential impurities observed using the new method. The Applicant also should provide a detailed description of the new analytical procedure with appropriate validation.
2. Alternative primary and/or secondary packaging should be used to protect the drug product from light. A description and justification for the new packaging system should be submitted

with appropriate letters of authorization. In addition, drug product labeling will need to be revised to state that the vials should be protected from light.

3. Based on the limited stability data provided in the Application and the out-of-specification (OOS) results for particulate matter observed at accelerated conditions, an expiration date of not longer than (NMT) (b) (4) would be appropriate for the drug product when stored at controlled room temperature, protected from light.

1.3 Post Approval Commitments (additional issues that would need to be addressed postmarketing, if the product were to be approved)

1.3.1 Clinical

1. The Applicant will need to complete the additional efficacy and safety study(ies) requested above under the description of clinical deficiencies (Section 1.2.1) as a condition of an approval under Subpart H 21 CFR 314.510 (see Item No. 1 above under clinical deficiencies) or as a formal Phase 4 commitment (see Item No. 2 above under clinical deficiencies).
2. Additional developmental assessment is needed of children at ages 18-24 months whose mothers had been treated with 17OHP-C. This assessment could be obtained from the offspring of women enrolled in the confirmatory efficacy study or the safety study addressing early fetal loss. Children who screen positive for developmental delay should have a formal psychometric assessment and an additional assessment by a neurologist.
3. Long-term post treatment safety data (at least through puberty) from children whose mothers had been treated with 17OHP-C are lacking in the NDA. This information needs to be obtained and could be obtained through the establishment of a surveillance program (e.g., a registry) to evaluate the effects of prenatal exposure in adolescents. The Applicant should submit a proposal as to how these data will be obtained.

1.3.2 Clinical Pharmacology

The following pharmacokinetic information should be obtained by the Applicant to allow for better understanding of 17OHP-C pharmacokinetics and optimal dosing:

- Characterization of the pharmacokinetics of 17OHP-C and its metabolites in pregnant women (including both plasma and urine concentrations) at several periods throughout pregnancy.
- Assessment of the effect of body weight on the pharmacokinetics of 17OHP-C.
- Analysis of the effects of known strong inducers or inhibitors of drug metabolizing enzymes on 17OHP-C pharmacokinetics.

1.4 Recommendation on Risk Management Steps

No risk management steps other than appropriate labeling are recommended at this time.

2. BACKGROUND

2.1 Prematurity (Preterm Birth): Public Health Significance and Available Therapies

Public Health Significance. Preterm birth, defined as delivery prior to 37 completed weeks of gestation, is a significant public health problem in the United States, with an increasing prevalence, currently affecting 12% of all births. Although there are a number of diagnostic tests

proposed to identify women at risk for preterm labor and medications used off-label to treat preterm labor, there are no data indicating a benefit on neonatal morbidity or mortality from any of these interventions. Rates of preterm birth in the United States differ profoundly among ethnic groups; the rate of preterm birth in non-Hispanic black births is twice as high as that of non-Hispanic white births.

Available Therapies. Currently there is no approved drug product in the United States for prevention of preterm birth; however, 17OHP-C is being compounded by pharmacists and is being used widely for prevention of preterm birth in women at high risk. The medical need for an approved drug product for prevention of preterm birth is particularly acute because there also are no approved drug products currently marketed in the United States for the treatment of preterm labor. Although several drug products with tocolytic properties (i.e., stopping uterine contractions) are used off-label for treatment of preterm labor, randomized controlled trials have failed to demonstrate that these drugs improve perinatal outcomes.

In 2003, the findings from a multicenter, randomized, vehicle-controlled, double-blind clinical trial of 17OHP-C in women at high risk for preterm birth were published.[1] This trial was sponsored by the National Institute for Child Health and Human Development (NICHD). The trial was conducted for the NICHD by the Maternal-Fetal Medicine Units (MFMU) Network, which at that time consisted of approximately 19 university-based clinical centers in the U.S. This study (hereafter referred to as Study 17P-CT-002) showed a reduction in preterm births $< 37^0$ weeks gestation in women with a prior spontaneous preterm birth (a population at high risk for a recurrent preterm birth). The clinical component of NDA 21-945 is based largely on the data from Study 17P-CT-002 and a follow-up safety study (Study 17P-FU).

2.2 Description of Drug Product

17α-hydroxyprogesterone caproate was approved by the Food and Drug Administration (FDA) in 1956 for use in pregnant women (NDA 10-347; Delalutin®). The approved indications included the treatment of habitual and recurrent abortion, threatened abortion, and post-partum "after pains." This approval was based largely on safety considerations in that it occurred prior to the FDA Drug Amendment of 1962, which required that drugs must have substantial evidence of efficacy in addition to evidence of safety in adequate and well-controlled trials. In 2000, the FDA withdrew approval for Delalutin. This action was taken at the request of the holder of the NDA. The action was not taken because of safety concerns.

2.3 Regulatory History

After data from Study 17P-CT-002 were published in the New England Journal of Medicine, Adeza met with the Division of Reproductive and Urologic Products (hereafter referred to as DRUP or the Division) to discuss the possibility of using these data as the basis for an NDA for 17OHP-C for the indication of prevention of preterm birth in pregnant women at high risk.

[1] Meis PJ et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 348: 2379-85, 2003.

Study 17P-CT-002, however, had not been designed as a clinical trial to support marketing approval of 17OHP-C for prevention of preterm birth. The Division conveyed several recommendations and concerns to the Applicant during this and subsequent meetings. These included the following:

- The primary endpoint for Study 17P-CT-002 was a reduction in preterm births at < 37 weeks gestation. Although preterm birth is generally defined as a birth prior to 37 weeks gestation, the clinical significance of preterm birth is more pronounced at and prior to 32 weeks gestation. In the U.S., infants born after 32 weeks have very low mortality rates, and relatively low long-term morbidity.
- The primary endpoint of Study 17P-CT-002 (a reduction in preterm births at < 37 weeks gestation) is a surrogate for neonatal/infant morbidity and mortality. The Division indicated that its assessment of effectiveness also would consider the demonstrated benefit of 17OHP-C on these latter outcomes, namely, overall survival of infants and a reduction in serious infant morbidities.
- There was the lack of follow-up data, beyond the period of initial hospital assessment, of children for whom their mother had received 17OHP-C for the prevention of preterm birth. The Division requested that the Applicant obtain follow-up developmental and safety data on children whose mothers had participated in Study 17P-CT-002 through at least 2 years of age.
- Normally, either 2 adequate and well-controlled studies or a single study with a robust and compelling outcome and strong supporting data would be required to support approval of a new drug product. There was a possibility that the data from Study 17P-CT-002 would not be sufficient to demonstrate that 17OHP-C is safe and effective for the prevention of preterm birth.

3. SCOPE OF INFORMATION DISCUSSED AND REVIEWED IN THIS MEMORANDUM

The primary Medical Reviewer (Barbara Wesley MD) and the clinical Team Leader (Lisa Soule MD) have each written clear and thorough reviews of the clinical information provided in the current submission. I fully concur with their independent conclusions and recommendations that NDA 21-945 receive an approvable action for the proposed indication of prevention of preterm birth in women with a history of at least one spontaneous preterm birth. Therefore, in the remainder of this Memorandum, I focus only on the efficacy and safety findings in the present submission that were of most importance in (1) my also concluding that NDA 21-945 is approvable for the proposed indication of "prevention of preterm birth in women with a history of at least one spontaneous preterm birth" and (2) my determination of the clinical deficiencies that would need to be satisfactorily addressed if this NDA were eventually to be approved.

4. OVERVIEW OF CLINICAL PROGRAM

In support of their Application, Adeza submitted data from 2 active treatment clinical trials and a follow-up safety study: Study 17P-IF-001; Study 17P-CT-002; and Study 17P-FU. An overview of these studies is presented in Table 1. All of the studies were sponsored by the NICHD. Studies 17P-IF -001 and 17P-CT-002 were to be conducted in accordance with identical designs. Each was a double-blind, vehicle-controlled clinical trial, randomized 2:1 to 17OHP-C or vehicle, which enrolled pregnant women with a prior history of at least 1 spontaneous preterm

birth. Treatment (a weekly injection of 250 mg 17OHP-C or vehicle) was initiated between 16^0 to 20^6 weeks gestation and continued through 36^6 weeks gestation or delivery, whichever occurred first.

Table 1 Clinical Studies of 17OHP-C in NDA 21-945

Protocol # / Status	Study Design	Study Population	Treatment Dose	Duration of Drug Treatment	Number of Subjects Enrolled	Number of Black/ Non-Black Subjects	Mean Age (Range)
17P-IF-001 Terminated Mar 1999[A]	Double-blind, Vehicle-controlled, Randomized 2:1 17OHP to Vehicle	Pregnant women with previous spontaneous preterm birth	250 mg 17OHP per week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 36^6 wks gestation or delivery	Total: 150 17OHP: 94 Vehicle: 56	Total: 95/55 17OHP: 54/40 Vehicle: 41/15	26.2 yr (17, 42)
17P-CT-002 Completed Aug 2002[B]	Double-blind, Vehicle-controlled, Randomized 2:1 17OHP to Vehicle	Pregnant women with previous spontaneous preterm birth	250 mg 17OHP per week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 36^6 wks gestation or delivery	Total: 463 17OHP: 310 Vehicle: 153	Total: 273/190 17OHP: 183/127 Vehicle: 90/63	26.2 yr (16, 43)
17P-FU Completed Nov 2005	Observational long-term safety follow-up for Study 17P-CT-002	Infants discharged live in Study 17P-CT-002	None	No study treatment was administered	Total: 278 17OHP: 194 Vehicle: 84	Total: 152/126 17OHP: 105/89 Vehicle: 47/37	47.4 mo (30, 64)

[A] Study 17P-IF-001 was terminated early by the Sponsor when the manufacturer recalled the study drug. The last subject visit was in August 1999. Of the 150 subjects, 104 subjects (65 randomized to 17OHP-C and 39 randomized to vehicle) had ended their treatment prior to the study termination either because they had completed treatment with study drugs completed study treatment to 36^6 weeks of gestation or delivery or had withdrawn prematurely for reasons other than recall of study drugs.

[B] An independent Data and Safety Monitoring Committee (DSMC) reviewed the study data after 400 subjects had completed the study. Based on that interim dataset, the primary endpoint, birth $<37^0$ weeks of gestation, was significantly reduced and the p-value was below the p-value specified in predefined stopping rules. The DSMC recommended that enrollment in the study be stopped, so that no new subjects would be assigned vehicle. By the time the study was stopped, 463 subjects had been enrolled, which was 92.5% of the proposed sample size of 500 subjects.

Source: Table 2, pg. 20 of primary Medical Review for NDA 21-945.

5. EFFICACY (PRIMARY STUDY 17P-CT-002)

5.1 Efficacy Endpoints and Objectives

Primary Endpoint. The primary objective of this study was to determine if treatment with 17OHP-C, initiated between 16^0 and 20^6 weeks gestation, compared with vehicle, reduced the risk of preterm birth (birth $<37^0$ weeks gestation) in women who had previously experienced a prior spontaneous preterm birth. All deliveries occurring from the time of randomization (which

occurred immediately before the first injection of study drug) through 36^6 weeks gestation, including miscarriages (i.e., spontaneous abortions) and stillbirths, were counted in the primary outcome. The primary endpoint was the proportion of subjects in each treatment group who delivered at $< 37^0$ weeks gestational age.

Secondary Objectives. The secondary protocol-defined objectives included both maternal and neonatal outcomes. These objectives included:

- Whether treatment with 17OHP-C reduces the use of tocolytic therapy and/or cervical cerclage.
- Whether treatment with 17OHP-C reduces neonatal morbidity/mortality.

Neonatal outcomes considered secondary efficacy measures included: birthweight; score reflecting condition of neonate (Apgar score); admission to the neonatal intensive care unit (NICU); infant hospital days; number of days of neonatal respiratory therapy; stillbirths; neonatal deaths; neonates with respiratory distress syndrome (RDS); intraventricular hemorrhage (IVH); bronchopulmonary dysplasia (BPD); necrotizing enterocolitis (NEC); early onset of neonatal sepsis; and seizures.

Based on a request by the Division, the following secondary endpoints were added to the analyses:

- Whether treatment with 17OHP-C, compared to vehicle, reduced the risk of preterm birth $< 35^0$ and $< 32^0$ weeks gestation.
- Whether treatment with 17OHP-C reduced overall neonatal morbidity/mortality based on a composite measure of neonatal morbidity and mortality. The composite was based on the proportion of infants who experienced one or more of the following: death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC.

Division Director's Comment

- *The Division made the request to determine the reduction in preterm births at <35 and <32 weeks gestation because of the increased morbidity/mortality associated with premature births at these ages.*

5.2 Subject Disposition

A total of 463 subjects were randomized at 19 study centers in the U.S. Of these 463, 126 were enrolled at a single center (University of Alabama). Enrollment at the other 18 centers ranged from 45 to 2 subjects per center.

Four hundred eighteen (418) subjects (90.3%) completed injections through 36^6 weeks gestation or delivery, whichever occurred first: 279 of 310 (90.0%) in the 17OHP-C group and 139 of 153 (90.8%) in the vehicle group. Early discontinuation of treatment occurred at a similar rate in both treatment groups (8.7% in 17OHP-C subjects vs. 9.2% in vehicle subjects). Most of these subjects discontinued treatment due to "non-clinical reasons" (which were not further defined by the Applicant) or physician discretion (6.7% in 17OHP-C group vs. 7.2% in vehicle group). Seven subjects (2.2%) in the 17OHP-C group and 4 subjects (2.6%) in the vehicle group terminated treatment because of adverse events. Four (1.3%) subjects, all in the 17OHP-C group were lost to follow-up.

5.3 Percentages of Preterm Births at < 37^0, < 35^0, < 32^0, and < 28^0 Weeks Gestational Age (FDA Analysis)

The percentages of preterm births, mean differences between treatment groups, and 95% confidence intervals (CIs) of the differences at < 37^0 weeks gestational age (protocol defined primary endpoint), and < 35^0, < 32^0, and < 28^0 weeks gestational age (secondary endpoints) are listed in Table 2. A lesser percentage of subjects in the 17OHP-C treatment group had preterm births at each of < 37^0, < 35^0, and < 32^0 weeks gestation. There was no difference between treatment groups for gestational ages of < 28^0 weeks.

Table 2 Proportion (95% Confidence Interval) of Subjects with Preterm Births at <37^0, <35^0, <32^0, and <28^0 Weeks Gestational age (FDA Analysis)

Gestation Age at Delivery	17OHP-C[A] (N=310)	Vehicle (N=153)	Mean Treatment Differences and 95% Confidence Interval [B]
	Percent of Preterm Births		
< 37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
< 35^0 weeks	21.3	30.7	-9.4% [-18.7%, -0.2%]
< 32^0 weeks	11.9	19.6	-7.7% [-16.1.%, -0.3%]
< 28^0 weeks	9.4	10.5	-1.1% [-7.4%, 5.2%]

[A] Four 17OHP-C treated patients were lost-to-follow-up. They are counted as deliveries at their gestational ages at time of last contact (18.6, 22.0, 34.4, and 36.6 weeks).
[B] To preserve the overall Type I error rate of 0.05, the adjusted confidence intervals (equivalent to a 96.6% confidence interval) use the final p-value boundary of 0.0345.
Source: Table 3.1, FDA statistical review, October 19, 2006.

Division Director's Comments

- *The differences in percentages of preterm births at < 37^0, < 35^0, and < 32^0 weeks gestation all met the generally accepted criteria for statistical significance based on the respective 95% confidence intervals after adjusting for the 2 interim analyses and the final analysis to preserve the overall Type I error rate of 0.05.*
- *The reduction in preterm births < 37 weeks was statistically persuasive, even after adjusting for the 2 interim analyses.*
- *The reductions in preterm births < 35 and < 32 weeks, although statistically significant, were not statistically persuasive for supporting approval of 17OHP-C based on the outcome of a single clinical trial. The statistical strength of the reductions in preterm births of < 35 and < 32 weeks are particularly important because these endpoints, but not a reduction of < 37 weeks, were considered by a majority of the members of the Advisory Committee for Reproductive Health Drugs to be a meaningful surrogate for a reduction in neonatal morbidity and/or mortality.*
- *The point estimates of the mean differences between the 2 treatment groups at each of < 37, < 35, and < 32 weeks is also an important consideration in assessing the potential clinical significance of the treatment effect. The mean differences at each of < 35 and < 32 weeks (-9.4% and -7.7%, respectively) were approximately one-half of that at < 37 weeks (-17.8%).*
- *Based on an analysis by the Applicant, the benefit of treatment for preterm birth of < 37 weeks gestation appeared to remain consistent over varying levels of maternal risk, as*

measured by maternal race, number of prior preterm births, and gestational age of qualifying preterm birth.

- *The rate of preterm birth < 37 weeks gestation in the vehicle group is higher than that typically reported in trials in a similar at risk population (e.g., preterm birth rates in other trials within the MFMU Network generally ranged from 35-40% in the control groups).*

5.4 Other Secondary Endpoints

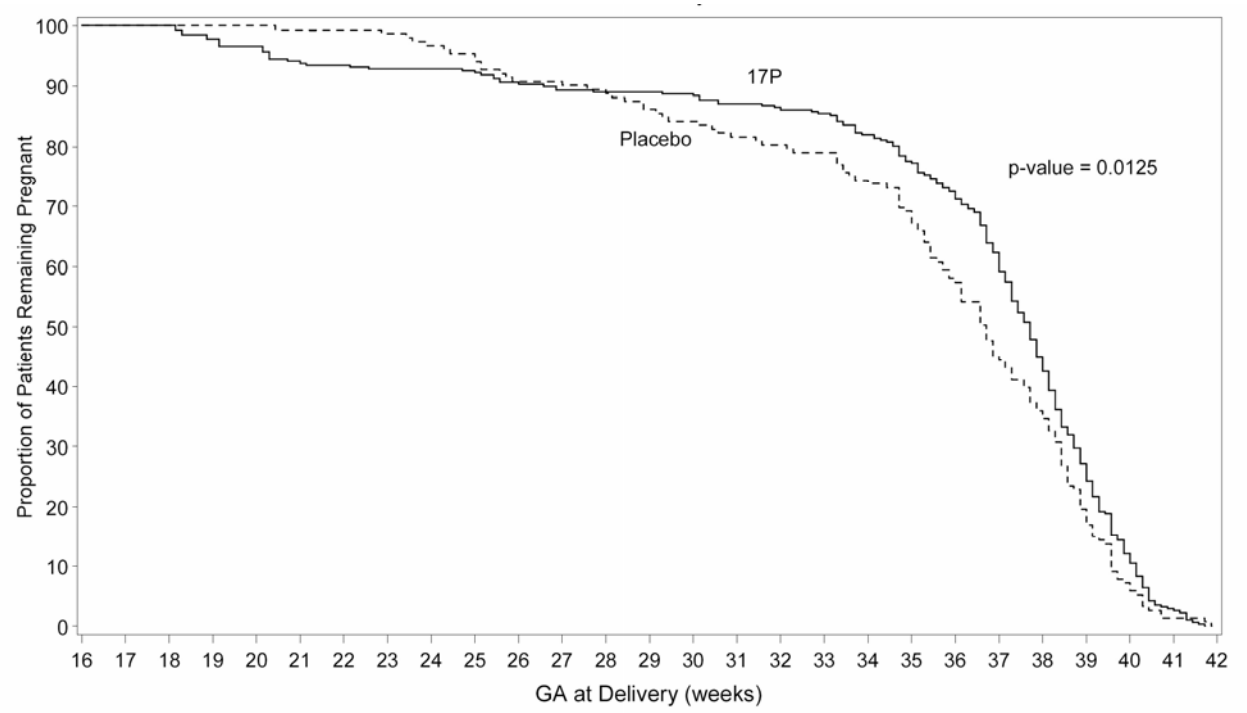
5.4.1 Mean Gestational Age at Delivery and Duration of Pregnancies (Applicant's Analysis)

The mean gestational age at delivery for subjects with available outcome data was one week greater in the 17OHP-C group (36.2 weeks vs. 35.2 weeks). The gestational ages at delivery ranged from 18.1 to 41.6 weeks. The median prolongation of pregnancy (defined as the time from randomization until delivery or date that the subject was last confirmed to be pregnant) was higher in the 17OHP-C group compared to the vehicle group (131 days vs. 125 days).

5.4.2 Proportions of Women Remaining Undelivered by Gestational Age

The Applicant provided a Kaplan Meier analysis of the time to delivery in the 2 treatment groups that showed a statistically significant difference in the shape of the curves by the log-rank test (see Figure 1).

Figure 1 Time to Delivery as a Function of Gestational Age, using Staggered Entry Based on the Gestational Age at Randomization (Study 17P-CT-002)



Source: Applicant's response to FDA's request dated 7/20/06.

The results of the log-rank test show that the difference in the shapes of the curves is statistically significant (p-value = 0.0125). Prior to approximately 25 weeks gestation, a numerically greater

proportion of subjects randomized to the 17OHP-C group delivered at each gestational age; after 28 weeks gestation, a greater proportion of subjects randomized to the vehicle group delivered at each gestational age.

Division Director's Comment

- *The increased proportion of delivered subjects in the 17OHP-C group, relative to the vehicle group, up to a gestational age of 25 weeks was due to 5 miscarriages (spontaneous abortions) in the 17OHP-C group and other early fetal losses. (See Section 5.4.3). Whether treatment with 17OHP-C contributed to these early pregnancy losses is not known.*

5.4.3 Miscarriages, Stillbirths, and Neonatal Deaths

The numbers of miscarriages, stillbirths, and neonatal deaths in each of the treatment groups are listed in (Table 3). Five of 306 subjects assigned to the 17OHP-C group experienced miscarriages. No subject in the vehicle group miscarried. The incidence of stillbirths also was slightly higher in the 17OHP-C group. Overall, 8 subjects had stillbirths: 6 subjects (2.0%) in the 17OHP-C group and 2 subjects (1.3%) in the vehicle group. The incidence of neonatal deaths was numerically twice as high in the vehicle group (5.9% vs. 2.6%), but the difference was not statistically significant. The overall incidence of fetal and neonatal mortality was similar in the 2 treatment groups (19 of 306 [6.2%] in the 17OHP-C group and 11 of 153 [7.2%] in the vehicle group).

Table 3 Miscarriages, Stillbirths, and Neonatal Deaths (Study 17P-CT-002)

Pregnancy Outcome	17OHP-C N=306 n (%) [A]	Vehicle N=153 n (%) [A]	Nominal P-value [B]
Miscarriages <20 weeks gestation	5 (2.4)[C]	0	0.17
Stillbirth	6 (2.0)	2 (1.3)	0.72
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.12
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.69**

[A] Percentages are based on number of enrolled subjects and not adjusted for time on drug.
[B] No adjustment for multiple comparisons.
[C] Percentage adjusted for the number of at risk subjects (n=211) enrolled at < 20 weeks gestation.
Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

Division Director's Comments

- *The trend towards a benefit in the reduction of neonatal death in the 17OHP-C group was off-set by a trend toward an increase in the rates of miscarriage and possibly stillbirth in the 17OHP-C group, resulting in no overall increase in survival in the 17OHP-C group.*
- *A similar trend toward an increase in the rates of miscarriage and possibly stillbirth associated with use of 17OHP-C was not observed in supportive Study 17P-IF-001 (see Table 9).*

- *Data on second trimester miscarriage rates also were available from 4 studies reported in a meta-analysis of published studies.[2] Data in the meta-analysis publication showed a possible trend toward an increased risk of miscarriage in the 17OHP-C groups of the 4 studies as compared to vehicle, but the trend did not approach statistical significance (odds ratio of 1.30, with 95% confidence interval of 0.61 – 2.74).*
- *The trend toward increased second trimester miscarriage in women treated with 17OHP-C should be investigated as a condition of approval.*

5.4.4 Neonatal Outcomes and Morbidities other than Death

Additional endpoints evaluated neonatal outcomes, including the proportions with birth weight of < 2500 and < 1500 g. The 17OHP-C group had a statistically significantly lower percent of < 2500 g infants (27% compared to 41% of vehicle-exposed neonates). The trend toward a lower proportion of < 1500 g infants (8.6% in the 17OHP-C group vs. 13.9% in the vehicle group) was not statistically significant. Mean birth weight was numerically, but not statistically greater in the 17OHP-C treatment group. There were no differences in mean 1 and 5 minute Apgar scores between offspring of 17OHP-C and vehicle-treated women. Neonatal intensive care unit (NICU) admission, NICU stay, and hospital stay also were compared; only NICU admission differed significantly between groups, with 28% of 17OHP-C exposed infants admitted vs. 36% of vehicle-exposed infants. Individual components of the mortality/morbidity composite endpoint also were assessed, as were other outcome measures such as use of supplemental oxygen. Of 15 measures of neonatal morbidity evaluated, 3 were statistically significantly different, favoring a treatment effect for 17OHP-C: use of supplemental oxygen (15% vs. 24%), any IVH (1.4% vs. 5.3%), and NEC (0 vs. 2.7%).

Division Director's Comment

- *The analyses of individual neonatal morbidity endpoints were not adjusted for multiple comparisons and may not represent true treatment effects.*

The Applicant also provided an assessment of the proportion of infants in each treatment group with one or more events making up a composite endpoint of neonatal morbidity/mortality (comprising death, RDS, BPD, grade 3 or 4 IVH, sepsis, or NEC). Although there was a lower proportion of subjects in the 17OHP-C group (11.9% vs. 17.2% in the vehicle group) who experienced at least one event of the composite endpoint, this difference was not statistically significant.

Division Director's Comment

- *The clinical trial was not powered to show a reduction in infant morbidity/mortality. The analysis of neonatal morbidity/mortality based on the composite endpoint was performed at the request of the Division.*

5.5 Additional Analyses Requested by FDA

Upon determination that the University of Alabama had contributed 27% of the sample size of Study 17P-CT-002, the Division requested that the Applicant provide a table analyzing the

[2] Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. *Brit J Obstet Gynecol* 97: 149-54, 1990

primary and key secondary endpoints for that single site, for all other sites, and for all centers. Results are presented in Table 4.

Table 4 Percentages of Preterm Births at < 37, < 35, and < 32 Weeks Gestation – Effect of Largest Center

Gestation (weeks)	Percentage of Preterm Births								
	University of Alabama			All Other Centers Combined			All Centers		
	17OHP-C (n=86)	Vehicle (n=40)	Diff.	17OHP-C (n=224)	Vehicle (n=113)	Diff.	17OHP-C (n=310)	Vehicle (n=153)	Diff.
< 37	26.7	45.0	***-18.3***	41.1	58.4	***-17.3***	37.1	54.9	***-17.8***
< 35	17.4	27.5	***-10.1***	22.8	31.9	***-9.1***	21.3	30.7	***-9.4***
< 32	10.5	25.0	***-14.5***	12.5	17.7	***-5.2***	11.9	19.6	***-7.7***

Source: Applicant's submission of October 10, 2006.

Division Director's Comment

- *Although the rates of preterm birth at < 37 and < 35 weeks gestation are numerically lower in both the 17OHP-C and vehicle groups at the University of Alabama than in all other centers combined, the differences in rates between 17OHP-C and vehicle groups are similar (-18.3% vs. -17.3%, respectively and -10.1% vs. -9.1%, respectively), suggesting a comparable treatment effect across centers. However, there is an apparent greater benefit of treatment at < 32 weeks at the Alabama site than in all other centers combined (-14.5% [Alabama] vs. -5.2% [other sites combined]). This apparent greater benefit is a consequence of a higher preterm birth rate in the vehicle group and lower birth rate in the 17OHP-C group at the Alabama site compared to the respective rates at < 32 weeks gestation of all other centers combined.*

The Applicant conducted several analyses to assess the possibility of a center effect including: an efficacy analysis with and without the University of Alabama site; a center by treatment interaction analysis using logistic regression; evaluation of consistency of treatment effect across centers using the Breslow-Day statistic; and an adjusted analysis for center using the Cochrane-Mantel-Haensel statistic. The efficacy analysis, with and without the University of Alabama, produced results identical to the table above. The Applicant noted that the treatment differences at < 32 weeks with (-7.7) and without (-5.2) the University of Alabama were similar, as were the relative risks of birth < 32 weeks (0.68 with and 0.70 without the University of Alabama). The remaining analyses according to the Applicant also indicated little likelihood that the effect at < 32 weeks was being "driven" by this single center.

Division Director's Comment

- *Although the Applicant's analyses appear satisfactory, the large contribution to the total sample size by a single site is of concern in an application that is relying upon a single clinical trial to demonstrate efficacy. These concerns further support my conclusion that a confirmatory trial is needed to evaluate whether the efficacy results, especially at < 32 weeks, can be replicated at different centers.*

5.6 Statistical Reviewer's Assessment

The Statistical Reviewer, Lisa Kammerman, Ph.D., included the following statements in the "Conclusions and Recommendations" of her review dated October 19, 2006:

From a statistical perspective, the level of evidence from Study 17P-CT002 is not sufficient to support the effectiveness of 17P. The primary reason is the absence of a second, confirmatory study. Without a second study, the generalizability of the study results to a larger population cannot be assessed.

The "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" sets forth guidance needed for the FDA to accept results from a single, clinical study. The guidance on clinical evidence stresses the importance of a large multi-center study to help establish the credibility of a single study submission and that the credibility is enhanced if no single center accounts for an unusually large proportion of the subjects.

When compared with all other centers, one center, the University of Alabama, is disproportionately represented in the study. The University of Alabama accounts for about 25% of all subjects enrolled (126/463) and is about three times the size of the next largest center, the University of Tennessee (45/463 = 9.7%).

When two studies are submitted, the chance of both studies yielding a false positive result is 1/1600. In the case of a single study, the results must be less than a nominal p-value of 0.00125 to ensure the same false positive rate. In Study 17P-CT-002, the only endpoint that meets this criterion is Delivery <37 weeks gestation. Deliveries at times earlier than 37 weeks gestation were not statistically significant at 0.001. The results of the analyses of the 32 and 35 week endpoints suggest their false positive rates could be as great as 1/40.

Because of the public health need for a drug product to prevent preterm deliveries, we might be willing to accept a false positive rate that is somewhat greater than 1/1600 if the results appear to be generalizable. However, because of the issues introduced by the size of the University of Alabama and its findings, together with the 1/40 false positive rates for the 32 and 35 week endpoints, I do not believe the study results can be generalized to a larger population.

Therefore, from a statistical perspective, I do not believe this study meets the level of evidence needed to support the efficacy of 17P.

Division Director's Comment

- *The recommended level of significance could also be achieved by conducting a confirmatory study. This will be addressed by exploring the feasibility of another clinical study as a condition of approval under Subpart H (see Section 1.2.1).*

5.7 Overall Assessment of Efficacy

The differences in percentages of preterm births between the 17OHP-C and vehicle treatment groups at < 37, < 35, and < 32 weeks gestation each met the generally accepted criteria for statistical significance in Study 17P-CT-002. The reduction in preterm births < 37 weeks was statistically persuasive, even after adjusting for the 2 interim analyses. The reductions in preterm births of < 35 and < 32 weeks, although statistically significant, were not sufficiently persuasive for supporting approval of 17OHP-C based on the outcome of a single clinical trial.

Results were consistent across all centers at < 37 and < 35 weeks. At < 32 weeks, however, there may be an interaction between center and treatment based on a greater difference between treatment groups (i.e., greater benefit of treatment with 17OHP-C) at the University of Alabama than was seen in the study as a whole or in all other centers combined. This suggests that the effect of 17OHP-C in prevention of preterm birth at < 32 weeks may not be consistent across centers.

The Kaplan-Meier analysis of time to delivery demonstrated a statistically significant difference between "survival" curves for the two treatment groups, reflecting a prolongation of pregnancy in the 17OHP-C group from about 28 weeks of gestation on, but an increased risk of preterm delivery from the time of enrollment to about 25 weeks of gestation.

Although there was a numerically lower rate of neonatal mortality in the 17OHP-C group, the increased rate of early fetal loss in this group led to an overall finding of no difference in fetal/neonatal mortality across the 2 treatment groups.

Other secondary outcome measures did not show a consistent pattern of benefit for treatment with 17OHP-C. In particular, measures of neonatal outcome generally did not differ between treatment groups; however, the study was not powered to detect such differences.

6. SAFETY FINDINGS

6.1 Primary Study 17P-CT-002

The primary Medical Reviewer has provided a thorough review of the safety findings from the Applicant's clinical trials in her review of NDA 21-925. Dr. Wesley did not identify any worrisome clinical safety findings in her review other than the possible relative increase in the percentage of miscarriages and stillbirths in the 17OHP-C group previously discussed (see Section 5.4.3). The following is therefore a summary of the most important safety findings.

There were no maternal deaths. Eleven subjects discontinued treatment because of an adverse event: 7 subjects were in the 17OHP-C group (3 with urticaria, 2 with injection site pain or swelling, 1 with arthralgia, and 1 with weight gain); 4 subjects were in the vehicle group (2 with pruritus, 1 with urticaria, and 1 with injection site pain). The most common serious adverse events (SAEs) were congenital anomalies. The numbers and types of these anomalies appeared evenly distributed over the 2 treatment groups. There were 3 reports of a SAE in the mothers, all in the 17OHP-C group; none were thought by the investigators to be related to the study drug. The SAEs were: one case of a pulmonary embolus 8 days after delivery; one case of cellulitis at the study medication site; and one case that included postpartum hemorrhage, respiratory distress, and endometritis.

The most common adverse events (and the percentage of subjects reporting them in the 17OHP-C group) were injection site pain (34.8%), injection site swelling (17.1%), urticaria (12.3%), pruritus (7.7%), injection site pruritus (5.8%), nausea (5.8%), and contusion (5.5%). The most common adverse events (and the percentage of subjects reporting them in the vehicle group) were injection site pain (32.7%), urticaria (11.1%), contusion (9.2%), injection site swelling (7.8%), pruritus (5.9%), and neonatal death (5.9%).

Division Director's Comments

- *Although Study 17P-CT-002 and supportive Study 17P-IF-001 were conducted under an IND, adverse events (AEs) were not captured in the typical manner for studies designed to support drug approval. Only adverse events that were considered serious or unexpected by the investigator were reported on study case report forms (CRFs). Assessment of severity or relationship of AEs to study drug was not made for non-serious AEs. This practice would result in underreporting of non serious AEs in both treatment groups. The primary Medical Reviewer did not consider this to be a significant issue in her overall assessment of the safety of 17OHP-C because serious or unexpected adverse events were collected in the usual manner. I concur with her conclusion.*
- *The primary Medical Reviewer stated in her review that "the number and type of congenital anomalies appear evenly distributed over the treatment arms. This rate of anomalies is consistent with the background rate for congenital anomalies in the general population of 2-3%." I concur with this assessment.*
- *The majority of AEs that clearly or possibly led to early discontinuation of treatment were injection site reactions, which occurred with both 17OHP-C and vehicle treatments. Two subjects, one in each treatment group, had possible allergic reactions.*
- *The adverse events that were associated with premature termination of treatment do not raise any concerns about the safety of 17OHP-C for the prevention of preterm birth.*

The primary Medical Reviewer identified 3 out of 9 complications of pregnancy reported by the Applicant in both the principal study (Study 17P-CT-002) and the supportive initial formulation study (Study 17P-IF-001) for which the percentages of affected subjects were numerically greater in the 17OHP-C treatment groups. Theses complications were gestational diabetes, oligohydramnios, and preeclampsia (see Table 5).

Table 5 Selected Pregnancy Complications: Studies 17P-CT-002 and 17P-IF-001

Pregnancy Complication	Study	17OHP-C N	17OHP-C (%)	Vehicle N	Vehicle (%)
Gestational Diabetes	CT- 002	17	(5.6)	7	(4.6)
	IF- 001	8	(8.6)	0	(0.0)
Oligohydramnios	CT- 002	11	(3.6)	2	(1.3)
	IF- 001	2	(2.2)	1	(1.9)
Preeclampsia	CT- 002	27	(8.8)	7	(4.6)
	IF- 001	6	(6.5)	2	(3.8)

Source: Table 22, primary Medical Review, dated October 18, 2006.

Division Director's Comment

- *The mean gestational age at the time of diagnosis of preeclampsia in the 17OHP-C group of study 17P-CT-002 was 35.6 weeks compared to 33.9 weeks in the vehicle group. The higher gestational age at birth of subjects in the 17OHP-C group could explain, in part, why there was a numerically higher percentage of preeclampsia in that group, as the incidence rises with increasing gestational age.*

6.2 Study 17P-FU (Follow-Up Safety Study of Children)

6.2.1 Overview of Study

Infants born to women enrolled in Study 17P-CT-002, who survived to be discharged from the nursery, were eligible for participation in the follow-up safety study (Study 17P-FU). The following is a brief review of the findings from this study that is described fully in the primary Medical Review.

The study collected data with a validated child development instrument (the Ages and Stages Questionnaire [ASQ]), a Survey Questionnaire concerning the health and development of the child, and a physical examination. All children were at least 2 years of age at the time of the follow-up assessments. The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received weekly intramuscular injections of 17OHP-C compared with vehicle in Study 17P-CT-002. Two hundred seventy eight (278) children were enrolled: 194 from the 17OHP-C group and 84 from the vehicle group of Study 17P-CT-002.

6.2.2 Primary Outcome: Findings from Age and Stages Questionnaire (ASQ)

The ASQ was completed for 275 children, 193 from the 17OHP-C group and 82 from the vehicle group. The age of the children at the time of completion of the ASQ ranged from 30 to 64 months; mean age at time of completion did not differ between the 17OHP-C and vehicle groups (47.2 vs. 48.0 months). The ASQ responses were categorized to assess communication, gross motor, fine motor, problem solving, and personal-social development. Using threshold scores (cutoffs) for normal development, the percentages of children who had scores below the cutoffs for the 5 areas of development were determined. Table 6 shows the percentage of children in each treatment group whose ASQ scores suggested developmental problems in at least one of the areas.

Table 6 Percentages of Children in Each Treatment Group Whose ASQ Scores Suggested Developmental Problems

	17OHP-C N=193		Vehicle N=82	
	n	%	n	%
Occurrence of score <cutoff on at least one developmental area	53	27.5	23	28.0
Area of Development				
Communication	22	11.4	9	11.0
Gross Motor	5	2.6	3	3.7
Fine Motor	40	20.7	15	18.3
Problem Solving	20	10.4	9	11.0
Personal-Social	7	3.6	1	1.2

Source: Table 12-2, Final Report for Study 17P-FU.

Division Director's Comment

- *The percentage of children who scored below the cutoff in at least one developmental domain was comparable in the 2 treatment groups (27.5% in the 17OHP-C group and 28.0%*

in the vehicle group [p=0.9206]). The proportions of children below the cutoff in each developmental domain also were similar across treatment groups.

6.2.3 Secondary Outcomes

Outcomes from the Survey Questionnaire. There were no meaningful differences between the groups. A slightly higher proportion of children in the vehicle group had a diagnosis of, or a reported problem with, inability to pay attention/learn, hearing, ability to walk/run/play, motor skills, activity level, or communication problems. The most commonly reported diagnoses or reported problems were inability to pay attention/learn, hearing impairment, and impairment in ability to walk/run/play.

Developmental delay based on both ASQ score and independent diagnosis. Because the purpose of the ASQ is to identify children who may require further evaluation, only some children will have confirmation of a developmental delay upon evaluation by a professional. The percentages of children evaluated on the ASQ who scored below the cutoff in a specific ASQ developmental area and had at least one reported diagnosis of developmental delay by a professional are listed in Table 7.

Table 7 Development Delay in Children from Study 17P-CT-002

Area of Development	17OHP-C n = 13	Vehicle n = 8
	Percent Affected	
Communication	4.7	8.5
Gross motor	1.6	2.4
Fine motor	5.2	3.6
Problem solving	2.6	6.1
Personal-social	2.6	1.2

Source: Page 73, primary Medical Review, dated Oct. 18, 2006.

Division Director's Comment

- *Thirteen (6.7%) of the 193 children in the 17OHP-C group and 8 (9.8%) of the 82 children in the vehicle group had an ASQ score below cutoff for at least one developmental area and a reported diagnosis of developmental delay (either in a specific area or overall). Based on this small number of children and the other assessments, there is no suggestion of any adverse effects on postnatal development in the children whose mothers had been treated with 17OHP-C during their pregnancy.*

6.3 Overall Assessment of Safety Findings

There is a signal of possible increased fetal loss in Study 17P-CT-002, consisting of higher rates of miscarriage and second trimester stillbirths in women treated with 17OHP-C. This finding was not seen in Study 17P-IF-001. The higher rate of early fetal loss resulted in no survival advantage in the 17OHP-C group, despite having a lower neonatal death rate.

There were no maternal deaths, or SAEs likely to be causally related to 17OHP-C. The rate of discontinuation of treatment because of adverse events was < 3% in both groups. Common adverse events typically involved injection site reactions, pruritus, and urticaria, seen in both groups.

Women treated with 17OHP-C had higher frequencies of gestational diabetes, oligohydramnios and preeclampsia, in both of Studies 17P-CT-002 and 17P-IF-001. It is unknown whether this is attributable to the longer duration of pregnancy in women receiving 17OHP-C.

There was no difference between the 17OHP-C and vehicle groups in the percentage of children who scored below the cutoff in at least one developmental area of the ASQ. The percentages of children who scored below the ASQ cutoff in each of the individual 5 developmental areas also were similar in the 17OHP-C and vehicle groups. Developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age mates in physical, mental, social/emotional, or speech development, was reported for a comparable percentage of children in the 17OHP-C and vehicle groups.

Division Director's Comment

- *Overall, there is no evidence of either harm or benefit on the development of children born to mothers treated with 17OHP-C during their pregnancies.*

7. STUDY 17P-IF-001 (SUPPORTIVE CLINICAL TRIAL)

7.1 Subject Disposition

A total of 150 subjects were randomized, 94 to 17OHP-C and 56 to vehicle. One hundred four (104) subjects (65 randomized to 17OHP-C and 39 randomized to vehicle) had ended their treatment prior to premature termination of the study, either because they (a) had completed treatment with study drugs through 36^6 weeks or delivery or (b) had terminated treatment prematurely for reasons other than the recall of study drugs. Fifty-seven (57) subjects in the 17OHP-C group and 29 subjects in the vehicle group completed treatment through 36^6 weeks or delivery.

7.2 Efficacy Findings

Primary Efficacy Outcome. The incidences of delivery < 37^0 weeks gestation for (1) the intent-to-treat (ITT) population, (2) the population for which data were available (all subjects other than those lost to follow up), and (3) those subjects whose treatment was not prematurely terminated because of recall of study drug are listed in Table 8. For each analysis population, the percentage of subjects with a delivery of < 37^0 weeks gestation was numerically higher in the 17OHP-C treatment group. None of the differences were statistically different.

Table 8 Number (Percentage) of Subjects with Delivery < 37^0 Weeks Gestation (Study-IF-001)

Analysis Population	17OHP-C		Vehicle	
	N	n (%)	N	n (%)
ITT population	94	39 (41.5)	56	20 (35.7)
All available data	93	38 (40.9)	54	18 (33.3)
Not withdrawn due to study termination	**65**	**28 (43.1)**	**39**	**15 (38.5)**

ITT population was all randomized subjects. Subjects with missing outcome data were classified as having a preterm birth <37^0 weeks (treatment failure).
Source: Table 9-3, pg 21, abbreviated Final Report for Study 17P-IF-001.

Division Director's Comments

- *The data obtained from the analysis population identified as "not withdrawn due to study termination" is of most value since all subjects in this population had the opportunity to complete a full course of treatment. However, because the potency and overall quality of the study drugs could not be assured, the efficacy data obtained from this prematurely terminated clinical trial is of limited value and must be interpreted with caution.*
- *The findings from this trial do not suggest any benefit of treatment with 17OHP-C in reducing the risk of a delivery < 37^0 weeks gestation.*

Miscarriages, Stillbirths, and Neonatal Deaths The numbers and percentages of miscarriages, stillbirths, and neonatal deaths in the ITT population in each treatment group are listed in Table 9.

Table 9 Number of Miscarriages, Stillbirths, and Neonatal Deaths (Study 17P-IF-001)

Fetal/Neonatal Deaths	17OHP-C N=93	Vehicle N=54
Miscarriages	1 (1.1)	1 (1.9)
Stillbirths	1 (1.1)	2 (3.7)
Neonatal deaths	2 (2.2)	0
Total	**4 (4.4)**	**3 (5.9)**

Source: Table 9-8, pg 28, abbreviated Final Report for Study 17P-IF-001.

Division Director's Comment

- *Although this study did not demonstrate any overall benefit for treatment with 17OHP-C in terms of reduction in overall mortality, there was no trend toward an increased rate of miscarriages or stillbirths in the 17OHP-C group as was seen in Study 17P-CT-002. However, because the potency and overall quality of the study drugs could not be assured, the data obtained from this prematurely terminated clinical trial is of limited value and must be interpreted with caution.*

7.3 Safety Findings

Among the subjects not impacted by recall of study drug, the reasons for not completing treatment in the 17OHP-C group were adverse event (n = 1), withdrawal for "not otherwise specified" non-clinical reasons (n = 6), and lost to follow up (n = 1). The reasons for not completing treatment in the vehicle group were adverse event (n = 2), withdrawal for "non-clinical reasons" (n = 6), and lost to follow up (n = 2). There were no noteworthy safety findings

other than the observation that the percentages of subjects with gestational diabetes (8.6% vs. 0.0%) and preeclampsia (6.5% vs. 3.8%) were numerically higher in the 17OHP-C treated subjects (see Table 5).

8. ADVISORY COMMITTEE RECOMMENDATIONS

The Advisory Committee for Reproductive Health Drugs (ACRHD) met on August 29, 2006 to discuss this Application. The primary Medical Review reports on the recommendations from this meeting in considerable detail, including the actual results of the voting for each question posed to the Committee (Section 8.5 of the primary Medical Review). The Advisory Committee was asked to vote on several issues that included the following.

Issue 1. *Is a reduction in preterm birth prior to 37, 35, or 32 weeks gestation an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity?*

- The Committee stated clearly that a reduction in preterm birth < 37 weeks was not an adequate surrogate (yes=5, no=16) but that reductions in preterm birth < 35 weeks (yes=13, no=8) and < 32 weeks (yes=20, n=1) were adequate surrogates.

Issue 2. *Do the data provide substantial evidence that (a) 17OHP-C prevents preterm birth earlier than either 35 or 32 weeks gestation and (b) 17OHP-C reduces fetal and neonatal mortality or morbidity?*

- The Committee (by a small majority) indicated that the data provided substantial evidence that 17OHP-C (a) prevents preterm birth < 35 weeks (yes=12, no=9) but not < 32 weeks (yes=7, no=14). The Committee also clearly stated that the data did not provide substantial evidence that 17OHP-C reduces fetal and neonatal mortality or morbidity (yes=2, no=19).

Issue 3. *Is further study needed to evaluate the potential association of 17OHP-C with increased risk of second trimester miscarriage and stillbirth and if so, should this information be obtained prior to approval for marketing or post approval?*

- The Committee was unanimous in its recommendation that further study was needed (yes=21, no=0) but a majority felt that this information could be obtained post approval (pre-approval=8, post approval=13).

Issue 4. *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?*

- A majority of the Committee voted that the existing safety data were sufficient to support marketing approval of 17OHP-C without the need for additional pre-approval safety data (yes=13, no=8).

Issue 5. *Would the Committee recommend post approval clinical trial(s) to investigate further safety or effectiveness?*

- The Committee was unanimous in its recommendation that post approval clinical trial(s) to investigate further safety and/or effectiveness be conducted (yes=21. no=0).

Division Director's Comments

- *Overall a majority of the Committee members indirectly expressed support for approval based on the following 3 votes:*
  - *Thirteen of the 21 members voted that a reduction in* preterm birth *< 35 weeks was an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity;*
  - *Twelve of the 21 members voted that the Applicant's data provided substantial evidence that 17OHP-C prevents* preterm birth *< 35 weeks gestation; and*
  - *Thirteen of the 21 members voted that the existing safety data were sufficient to support marketing approval of 17OHP-C without the need for additional pre-approval safety data*
- *The committee was unanimous in recommending that further study was needed to evaluate the potential association of 17OHP-C with increased risk of second trimester miscarriage and stillbirth, but a majority (13 of 21 members) stated that this information could be obtained post approval.*
- *These recommendations would support approval under the sub-part H regulation because approval would be based on a surrogate of infant morbidity and mortality.*

9. BASIS FOR "APPROVABLE" REGULATORY ACTION

9.1 Efficacy Consideration

9.1.1 Quantity of Evidence Necessary to Support Effectiveness of a Drug Product

The current Application provides data from a single multicenter, vehicle-controlled trial to support the efficacy of 17OHP-C for the prevention of recurrent preterm birth. The FDA's Guidance Document entitled *Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)* discusses the usual requirement that effectiveness of a drug product be established by "two adequate and well-controlled studies, each convincing on its own." The Guidance further states that "reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible."

Given the widespread use of compounded 17OHP-C in pregnant women at increased risk of preterm birth, some experts believe that a vehicle-controlled trial is no longer feasible. Some experts also believe that the body of evidence in support of the effectiveness of 17OHP-C for reducing the risk of preterm birth is sufficiently compelling that a vehicle-controlled clinical trial would be unethical. These latter experts appear to have based their assessment of the effectiveness largely on the findings from Study 17P-CT-002 that were published in the New England Journal of Medicine in 2003. Several earlier publications describing the findings from small clinical trials, particularly the publication by Johnson et al., also have shown trends that support the effectiveness of 17OHP-C in reducing the risk of preterm birth.[3] However, other

[3] Johnson JW et al. Efficacy of 17α-hydroxyprogesterone caproate in the prevention of premature labor. *N Engl J Med*. 293: 675-80, 1975.

experts, including the Committee on Obstetrical Practice of the American College of Obstetrics and Gynecology, have stated that further study is warranted to identify the optimal dosing regimen and route of administration, as well as to explore further the long-term safety of 17OHP-C.[4]

9.1.2 Evidence of Effectiveness for 17OHP-C for Prevention of Preterm Birth

The differences in percentages of preterm births between the 17OHP-C and vehicle treatment groups at < 37, < 35, and < 32 weeks gestation in Study 17P-CT-002 each met the generally accepted criteria for statistical significance. The reduction in preterm births < 37 weeks was statistically persuasive, even after adjusting for the 2 interim analyses. The reductions in preterm births of < 35 and < 32 weeks, although statistically significant by generally accepted criteria, were less persuasive.

The clinical and statistical reviewers of this Application have raised questions as to whether the evidence of efficacy from this single Phase 3 study is adequate and sufficiently convincing to support approval. The clinical trial data did not provide evidence of a statistically significant effect on a composite endpoint of major neonatal morbidities and neonatal mortality. However, a majority of the members of the ACRHD believed that preventing preterm birth at < 35 and < 32 weeks of gestation represents an adequate surrogate for a reduction in neonatal morbidity and mortality. A majority of committee members also thought that there was a significant reduction in preterm births < 35 weeks gestation in Study 17-CT-002. However, the level of statistical significance for the treatment effect at <35 weeks and <32 weeks gestation does not meet the level of statistical significance generally expected by the FDA to support approval of a drug product based on the findings from a single clinical trial. There also remains some uncertainty as to whether the demonstrated benefit of 17OHP-C in prevention of preterm birth at < 32 weeks was due largely to the findings from a single large study site; if so, the benefit may not be generalizable to the proposed target population.

9.2 Safety Considerations

There were no significant safety findings from Study 17P-CT-002, supportive Study 17P-IF-001, and follow-up Study 17P-FU that would preclude approval of 17OHP-C for the proposed indication. The clinical finding of concern was an increase in early pregnancy loss in the 17OHP-C treated subjects. There was a trend toward an increase in second trimester miscarriage rate (pregnancy loss prior to 20 weeks of gestation) and a suggestion of an increase in stillbirth rate (death of the fetus prior to or during delivery) in the 17OHP-C group. These findings were presented to the members of the ACRHD. The recommendation of the majority of the members was that this observation required further investigation, but the investigation could be conducted post approval. A majority of the committee members also voted that no additional clinical safety data were required prior to approval.

Division Director's Comment

- *I concur with both of the recommendations of the majority of the committee members.*

Another potential area of concern is the absence of multigenerational reproductive toxicology data for 17OHP-C. The toxicology Team Leader recommended in her review that the Applicant

[4] ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 291, November 2003.

conduct a study to assess potential effects of 17OHP-C on developmental and reproductive parameters, including learning, behavior, and reproductive function in offspring exposed *in utero*. The toxicology and clinical reviewers all believed that the results of such a study need to be reviewed by the Division prior to possible drug approval.

Division Director's Comment

- *I concur with the recommendation of the toxicology and clinical reviewers.*

9.3 Recommended Action regarding Approvability

The public health importance of preterm birth and the lack of an approved efficacious treatment must be considered in weighing the benefit-to-risk ratio for a drug proposed for the indication of prevention of recurrent preterm birth. The fact that 17OHP-C is being compounded and used widely, with little or no regulatory oversight of compounding and no formal mechanism for monitoring of treatment-related adverse events, also are considerations.

Based on the clinical data in this Application, other published clinical data, published preclinical data, and public health consideration, I believe that the Application should receive an approvable action. Although the Applicant has demonstrated efficacy of 17OHP-C for reducing the risk of preterm birth at gestational ages that correlate with increased neonatal morbidity and mortality in a single Phase 3 trial, the data are not sufficiently robust or compelling to support approval at this time. The Applicant should submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of 17OHP-C for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510. If a vehicle-controlled trial is determined not to be feasible, the Applicant should provide alternative study design proposals. Even if a vehicle-controlled trial were not feasible, assurance that further study to determine the long-term safety of prenatal exposure to 17OHP-C, as well as to elucidate if 17OHP-C treatment is associated with increased fetal mortality, is necessary.

The absence of multigenerational reproductive toxicology data also precludes approval of this Application at this time

If 17OHP-C were to be approved without additional clinical trial efficacy data, approval under Subpart H 21 CFR 314.510 is recommended (see Section 1.2.1 and Section 1.3.1). Both the clinical and non-clinical (toxicology) deficiencies will need to be addressed in the Applicant's Complete Response as described in Section 1.2.1 and Section 1.2.2 of this Memorandum.

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/s/

Scott Monroe
10/21/2006 10:26:36 PM
MEDICAL OFFICER

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS
CLINICAL TEAM LEADER MEMORANDUM

NDA	**21-945**
Type of Application	**Original**
Applicant	**Adeza Biomedical**
Proprietary Drug Name	**Gestiva**
Established Drug Name	**17-α-hydroxyprogesterone caproate**
Drug Class	**Progestogen**
Indications	**Prevention of preterm birth in women with a history of at least one spontaneous preterm birth**
Route of Administration	**Intramuscular injection**
Dosage Form	**Injectable**
Dosage Strength	**250 mg**
CDER Receipt Date	**April 20, 2006**
PDUFA Goal Date	**October 20, 2006**
Date of Memorandum	**October 19, 2006**
Reviewer	**Lisa M. Soule, M.D.**

1 RECOMMENDATIONS

1.1 RECOMMENDATION REGARDING APPROVABILITY

I recommend that NDA 21-945 (Gestiva, 17-α-hydroxyprogesterone caproate) receive an approvable action for the indication of prevention of preterm birth in women with a history of at least one spontaneous preterm birth.

1.2 BASIS FOR RECOMMENDATION REGARDING APPROVABILITY (RISK/BENEFIT ANALYSIS)

The current submission provides data from a single multicenter controlled trial, using an endpoint that is a surrogate for neonatal morbidity and mortality, to support the safety and efficacy of 17 α-hydroxyprogesterone caproate (17OHP-C) for the prevention of recurrent preterm birth. The *Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998 discusses FDA's usual requirement that effectiveness of a drug be established by "two adequate and well-controlled studies, each convincing on its own[1]." The

Guidance further states that "reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible."

In the case of NDA 21-945, the clinical and statistical reviews have raised questions as to whether the evidence of efficacy from this single study is convincing and compelling. The clinical trial data did not provide evidence of a clinically meaningful or statistically significant effect on neonatal morbidity or mortality, as measured by a composite endpoint. However, preterm birth can be considered "a disease with potentially serious outcome," and the trial did succeed in demonstrating efficacy of 17OHP-C in preventing preterm birth at <35 and <32 weeks of gestation, cutpoints which the majority of members of the Advisory Committee on Reproductive Health Drugs believed represented adequate surrogates for fetal/neonatal mortality and neonatal morbidity. There remains some uncertainty as to whether the demonstrated benefit of 17OHP-C in prevention of preterm birth at <32 weeks was due largely to the findings from a single large study site, or whether this result generalizes.

The next question is then whether a confirmatory trial would be practically or ethically impossible. Given the widespread use of compounded 17OHP-C in pregnant women at increased risk of preterm birth, many experts argue that a placebo-controlled trial is no longer ethical or feasible. However, other experts, including the Committee on Obstetrical Practice of the American College of Obstetrics and Gynecology, have stated that further study is warranted to identify the optimal dosing regimen and route of administration, as well as to explore further the long-term safety of 17OHP-C[2].

In addition, the clinical data suggest that there may be more immediate safety issues, particularly involving increased early fetal loss in women treated with 17OHP-C, a finding that mirrors nonclinical data relating high doses of 17OHP-C with increased embryolethality in mice, rats and monkeys.

Therefore, I conclude that, while the Applicant has demonstrated efficacy of 17OHP-C in a single trial in reducing the risk of preterm birth at gestational ages that correlate with increased neonatal morbidity and mortality, these data are not sufficiently robust to support approval at this time. At a minimum, it needs to be determined whether a randomized, controlled confirmatory trial could be undertaken and successfully completed. Even if a placebo-controlled trial were not feasible, further study to determine the long-term safety of prenatal exposure to 17OHP-C, as well as to elucidate the signal of possible increased fetal mortality, is necessary.

The following deficiencies need to be addressed before this application could be approved:

- Submission of results of a multigenerational reproductive toxicology study designed to assess potential effects on developmental and reproductive parameters, including learning, behavior and reproductive function in offspring exposed *in utero*
- Resolution of issues relating to photostability, packaging and expiry, as identified in the Chemistry review dated September 22, 2006
- Evaluation of the feasibility of conducting an additional, multicenter, controlled trial to provide supportive evidence of safety and efficacy of 17OHP-C for the prevention of recurrent preterm birth. Such a study might be conducted as a phase 4 commitment or as part of a Subpart H approval. The study would need to address the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly, or through a well-established surrogate, such as the rate of preterm birth prior to 35 and 32 weeks of gestation. This or another study would also need to evaluate the potential association of 17OHP-C with increased early fetal loss (second trimester miscarriage and stillbirth).

1.3 RECOMMENDATION ON RISK MANAGEMENT STEPS AND/OR PHASE 4 STUDIES

1.3.1 Risk Management Steps

No risk management steps are recommended in this review cycle.

1.3.2 Phase 4 Studies

As noted above, further study of 17OHP-C is recommended. Optimally, a confirmatory randomized, placebo-controlled trial would be conducted to provide further evidence of efficacy on a meaningful clinical endpoint such as a composite endpoint of reduced neonatal mortality and morbidity. It is unclear at this point whether such a trial is feasible given extensive use of compounded 17OHP-C for prevention of preterm labor in at-risk women. Alternate designs or evaluations of the drug in slightly different populations might be pursued if it is concluded that a placebo-controlled trial in women with prior preterm birth would not be ethical or feasible.

Given the immense public health significance of preterm birth, coupled with the absence of effective treatment of preterm labor or other strategies effective at preventing preterm birth, Subpart H approval (21 CFR Part 314, Subpart H) may be an appropriate mechanism by which to approve 17OHP-C while awaiting further confirmatory evidence of its efficacy and safety. The utility of considering a Subpart H approval vs. requiring additional study as a phase 4 commitment can be evaluated once the deficiencies noted above are addressed in a Complete Response submission.

The Clinical Pharmacology reviewer also identified pharmacokinetic (PK) issues that need further elucidation, including PK at various periods of pregnancy, exposure-response relationships, effects of hepatic impairment, and impact of hepatic enzyme inducers/inhibitors. It is recommended that these issues be addressed in any future clinical trial of 17OHP-C.

2 BACKGROUND

Preterm birth, defined as delivery prior to 37 completed weeks of gestation, is a significant public health problem in the United States, with an increasing prevalence, currently affecting 12% of all births. Although there are a number of diagnostic tests proposed to identify women at risk for preterm labor and medications used off-label to treat preterm labor, there are no data indicating a benefit on neonatal morbidity or mortality from any of these interventions.

The National Institute of Child Health and Human Development (NICHD) initiated a multicenter, double blind, 2:1 randomized, vehicle-controlled clinical trial through its Maternal-Fetal Medicine Units (MFMU) Network in 1998 to evaluate the safety and efficacy of 17OHP-C in pregnant women with a history of spontaneous preterm birth. The initial trial (hereinafter referred to as 17P-IF-001) was terminated after about one year when the study drug was recalled by its manufacturer at the request of the FDA, due to violations of manufacturing processes that potentially could affect drug potency. At termination, only 150 of 500 planned women had been randomized, and only 86 women (57 of 17OHP-C treated women and 29 of vehicle treated women) had completed treatment.

The trial was started anew (referred to as 17P-CT-002) and enrolled 463 of a planned 500 women before being terminated prematurely due to crossing the prespecified threshold for efficacy as determined by the Data Safety Monitoring Board. Results of the trial were published in the New England Journal of Medicine in June 2003[3]. The American College of Obstetrics and Gynecology issued a Committee Opinion[2] in November 2003 stating that "further studies are needed to evaluate the use of progesterone in patients with other high-risk obstetric factors, such as multiple gestations, short cervical length, or positive test results for cervicovaginal fetal

fibronectin. When progesterone is used, it is important to restrict its use to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug." However, this opinion was viewed as supportive of the use of 17OHP-C for prevention of recurrent preterm birth, and use of compounded 17OHP-C has increased substantially since 2003.

2.1 DESCRIPTION OF PRODUCT

The drug substance (17OHP-C) was approved in 1956 under NDA 10-347 (with additional indications approved in 1972 under NDA 16-911) and marketed under the trade name Delalutin® for a variety of gynecological indications as well as for prevention of habitual, recurrent and threatened miscarriage. The sponsor discontinued marketing in the 1990's, and the NDAs were withdrawn "without prejudice" by the Agency in 2000. However, particularly since the publication of the 2003 New England Journal of Medicine article, 17OHP-C has been compounded by pharmacists and used in women at risk of preterm birth.

Team Leader Comment:

- ***Delalutin® was not withdrawn from the market due to safety concerns, nor were efficacy concerns noted at the time of withdrawal.***

The proposed dosing regimen is a weekly 1 mL intramuscular injection of 250 mg of 17OHP-C in castor oil with 46% benzyl benzoate and 2% benzyl alcohol, beginning at 16 weeks 0 days (16^0) to 20 weeks 6 days (20^6) weeks gestation and used through 36^6 weeks gestation or birth.

2.2 REGULATORY HISTORY

Adeza Biomedical submitted an IND (68,108) and met with the Division of Reproductive and Urologic Products (hereinafter referred to as the Division) on January 30, April 5 and July 16, 2004 to discuss the possible submission of a 505(b)(2) application based upon the NICHD trial. Issues of concern in these discussions that were conveyed to Adeza included:

- The Division did not agree that adequate replicate evidence of the safety and effectiveness of 17OHP-C for the prevention of recurrent preterm birth existed in the literature.
- Usually, either two adequate and well-controlled studies or a single study with a robust and compelling outcome and strong supporting data would be required to support approval of a new drug product. Data from the NICHD trial might not suffice to demonstrate the safety and effectiveness of 17OHP-C.
- The utility of the published study's primary endpoint, reduction of preterm birth at <37 weeks of gestation; the Division believed that delivery at <32 weeks was more clinically important, as the majority of neonatal morbidity and mortality occurs in infants born at <32 weeks. In addition, the Division would focus on reduction of morbidity and mortality, rather than on increasing the gestational age at delivery without any associated clinical benefit.
- Absence of follow-up data of children exposed *in utero* to 17OHP-C was noted; follow-up of at least 35-50% of babies in each treatment arm through at least two years of age was requested.
- Data from Study 17P-IF-001 should also be submitted in the NDA, as should all literature addressing the use of 17OHP-C for prevention of recurrent preterm birth.

A pre-NDA meeting was held on June 27, 2005. At that time, the Applicant was informed that:

- If additional clinical studies were conducted, sparse PK sampling might be needed to address unanswered PK issues

- Absence of certain information on adverse events (such as relationship to treatment and severity) would be a review issue
- The Division would grant Fast Track designation for this application
- The application would likely be presented to an Advisory Committee

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Barbara Wesley, stated in her review dated October 18, 2006:

> *This reviewer recommends an approvable action for Gestiva [17α-hydroxyprogesterone caproate or 17OHP-C] for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth. This recommendation is based on one multicenter clinical trial showing statistically significant reductions in preterm birth (PTB) at <35 and < 32 weeks gestation, surrogate endpoints recommended by an Advisory Committee to predict reduction in neonatal mortality and morbidity. Additionally, although previous studies are small, the data from the literature consistently demonstrates a decrease in PTB when women with a previous PTB or miscarriage are treated with 17OHP-C.*
>
> *Approval is contingent on the following:*
>
> - *Reassuring data from a multi-generational reproductive toxicology study for 17OHP-C.*
>
> *Approval is also contingent on the following as a post approval commitment:*
>
> - *Safety studies to assess to potential association of 17POH-C with miscarriages/ stillbirths, and long term safety evaluations of children at age 18-24 months and during adolescence.*
> - *Additional data to provide further statistical support for the effectiveness of 17OHP -C to reduce the incidence of preterm birth (PTB) particularly at <35 and <32 weeks gestational age.*

Team Leader Comment:

- ***I concur with the primary medical officer in recommending that Gestiva receive an approvable action.***

3 PREVENTION OF PRETERM BIRTH IN WOMEN WITH A HISTORY OF AT LEAST ONE SPONTANEOUS PRETERM BIRTH

3.1 OVERVIEW OF CLINICAL PROGRAM

The Applicant submitted data from two NICHD trials, 17P-IF-001 and 17P-CT-002. At the Division's request, the NICHD also conducted a follow-up study of infants delivered to mothers enrolled in 17P-CT-002 (this study is referred to as 17P-FU). The studies are outlined in Table 1.

Table 1 Clinical Studies of 17OHP-C in NDA 21-945

Protocol # /Status	Study Design	Study Population	Treatment Dose	Duration of Drug Treatment	Number of Subjects Enrolled	Number of Black/Non-Black Subjects	Mean Age (Range)
17P-IF-001 Terminated Mar 1999[A]	Double-blind, Placebo-controlled, Randomized 2:1 active treatment to Placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 37^0 wks gestation or delivery	Total: 150 17P: 94 Placebo: 56	Total: 95/55 17P: 54/40 Placebo: 41/15	26.2 yr (17, 42)
17P-CT-002 Completed Aug 2002[B]	Double-blind, Placebo-controlled, Randomized 2:1 active treatment to Placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 37^0 wks gestation or delivery	Total: 463 17P: 310 Placebo: 153	Total: 273/190 17P: 183/127 Placebo: 90/63	26.2 yr (16, 43)
17P-FU Completed Nov 2005	Observational long-term safety follow-up for Study 17P-CT-002	Infants discharged live in Study 17P-CT-002	None	No study treatment was administered	Total: 278 17P: 194 Placebo: 84	Total: 152/126 17P: 105/89 Placebo: 47/37	47.4 mo (30, 64)

[A] Study 17P-IF-001 was terminated early by the Sponsor when the manufacturer recalled the study drug. The last subject visit was in August 1999. Of the 150 subjects, 104 subjects (65 randomized to 17OHP-C and 39 randomized to vehicle) had ended their treatment prior to the study termination either because they had completed treatment with study drugs completed study treatment to 36^6 weeks of gestation or delivery or had withdrawn prematurely for reasons other than recall of study drugs.

[B] An independent Data and Safety Monitoring Committee (DSMC) reviewed the study data after 400 subjects had completed the study. Based on that interim dataset, the primary endpoint, birth $<37^0$ weeks of gestation, was significantly reduced and the p-value was below the p-value specified in predefined stopping rules. The DSMC recommended that enrollment in the study be stopped, so that no new subjects would be assigned placebo. By the time the study was stopped, 463 subjects had been enrolled, which was 92.5% of the proposed sample size of 500 subjects.

Source: Prepared by Medical Reviewer from final Study Reports.

Study 17P-IF-001 ran for a year before being terminated as discussed above, after enrolling 150 women of 500 planned. The data are discussed here and in Dr. Wesley's review, but have not been accorded a great deal of weight due to the premature termination of the study and to questions about the potency of the active study drug used.

Study 17P-CT-002 provided the primary efficacy and safety data for NDA 21-945. This trial, a 2:1 randomized, double-blind, multicenter, vehicle-controlled study, enrolled 463 women of 500 planned (310 to 17OHP-C and 153 to vehicle). Women meeting the inclusion and exclusion criteria had to have a previous spontaneous singleton preterm birth, be between 16^0 and 20^6 weeks of gestation in the current pregnancy, and not have known major fetal anomaly, maternal medical/obstetrical complications or a current or planned cerclage.

Study 17P-FU is discussed under the Safety section of this Memorandum.

3.2 DEMOGRAPHICS

Demographic and baseline characteristics of subjects in **Study 17P-CT-002** were comparable between treatment groups (Table 2). This was also true in **Study 17P-IF-001**.

Table 2 Demographic and Baseline Characteristics – Study 17P-CT-002

Characteristic	17P (N=310)	Placebo (N=153)	P-value
Age, yr			0.2481[d]
Mean (SD)	26.0 (5.6)	26.5 (5.4)	
Min, Max	16, 43	16, 40	
Race or ethnic group, n (%)[a]			0.8736[b]
African American	183 (59.0)	90 (58.8)	
Caucasian	79 (25.5)	34 (22.2)	
Hispanic	43 (13.9)	26 (17.0)	
Asian	2 (0.6)	1 (0.7)	
Other	3 (1.0)	2 (1.3)	
Marital status, n (%)			0.6076[b]
Married or living with partner	159 (51.3)	71 (46.4)	
Divorced, widowed, or separated	32 (10.3)	18 (11.8)	
Never married	119 (38.4)	64 (41.8)	
Pre-pregnancy BMI (kg/m^2)			0.3310[d]
Mean (SD)	26.9 (7.9)	26.0 (7.0)	
Min, Max	15.2, 72.2	16.1, 50.7	
Years of education			0.2175[d]
Mean (SD)	11.7 (2.3)	11.9 (2.3)	
Min, Max	2, 16	3, 16	
Diabetes, n (%)	13 (4.2)	4 (2.6)	0.3954[b]
Smoked cigarettes during pregnancy, n (%)	70 (22.6)	30 (19.6)	0.4647[b]
Alcoholic drinks during pregnancy, n (%)	27 (8.7)	10 (6.5)	0.4172[b]
Used street drugs during pregnancy, n (%)	11 (3.5)	4 (2.6)	0.7822[c]

[a] Race was self-assigned by the women.
[b] P-value from the chi-square test.
[c] P-value from the Fisher's Exact test.
[d] P-value from the Wilcoxon Rank Sum test.

Source: Primary Medical Review, p 81, based on Table 11-1, Final Study Report for Study 17P-CT-002

A total of 19 centers in the MFMU Network enrolled women in Study 17P-CT-002, with between 2-126 subjects enrolled per center. One center, the University of Alabama, contributed 27% of subjects. The next four largest centers each provided between 7.8 to 9.7% of subjects.

Team Leader Comment:

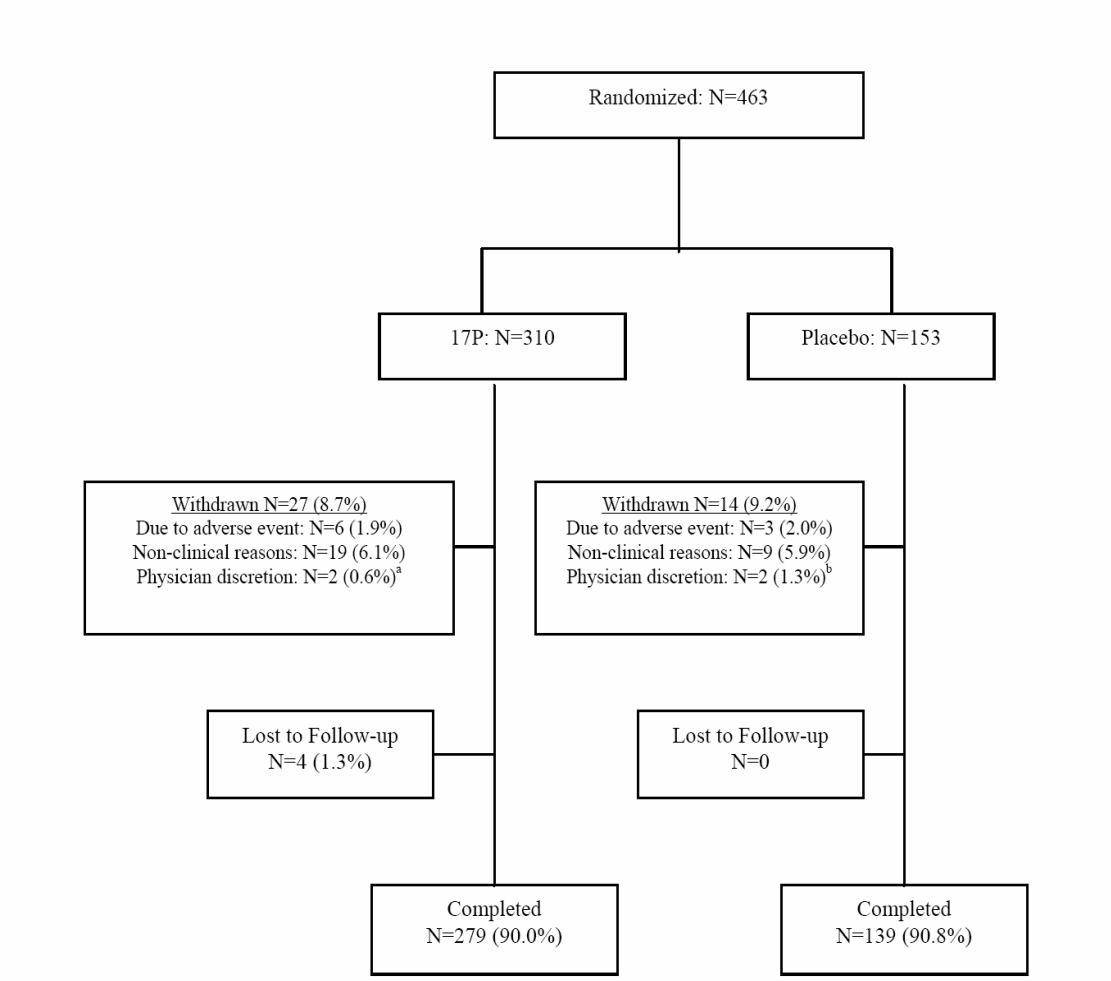
- ***The Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products notes that one characteristic of a single study that could provide adequate support for an effectiveness claim is that "(1) no single study site provided an unusually large fraction of the patients and (2) no single investigator or site was disproportionately responsible for the favorable effect seen." The significant contribution of the University of Alabama to the overall***

sample size may violate condition (1). Condition (2) is further discussed in Section 3.4.4.

3.3 DISPOSITION OF SUBJECTS

In **Study 17P-CT-002**, 279 subjects in the 17OHP-C arm (90%) and 139 in the vehicle arm (91%) completed the study. In the 17OHP-C arm, 27 subjects withdrew from treatment, but remained in the study to provide outcome data, and four were lost to follow-up. In the vehicle arm, 14 subjects withdrew from treatment but provided outcome data. Of subjects withdrawing from treatment, six (22%) of those from the 17OHP-C arm withdrew due to an adverse event, as did three (21%) of those in the vehicle arm. These data are displayed graphically in Figure 1.

Figure 1 Subject Disposition – Study 17P-CT-002



Source: Section 10.1, Figure 10-1, Final Study Report for Study 17P-CT-002

3.4 EFFICACY FINDINGS

3.4.1 Assessment of Efficacy

Efficacy was evaluated primarily based on the data from Study 17P-CT-002, as the value of Study 17-IF-001 was severely limited by its premature termination and the questionable potency of the study drug. The Applicant also provided literature citations addressing the safety and efficacy of 17OHP-C for prevention of preterm labor. These are discussed in detail in Dr. Wesley's review. In addition to the NICHD study published in the New England Journal of

Medicine, six other studies have evaluated the efficacy of 17OHP-C for prevention of preterm birth. Five of the studies were randomized, and all but one evaluated women at high risk for preterm birth (most often due to prior preterm deliveries). All studies except the one assessing non-high risk women showed a decreased rate of preterm birth in women treated with 17OHP-C as compared to placebo-treated women.

3.4.2 Principal Efficacy Study

Study 17P-CT-002 provided the primary efficacy and safety data for NDA 21-945. This trial, a 2:1 randomized, double-blind, multicenter, vehicle-controlled study, enrolled 463 women of 500 planned (310 to 17OHP-C and 153 to vehicle). Women meeting the inclusion and exclusion criteria had to have a previous spontaneous singleton preterm birth, be between 16^0 and 20^6 weeks of gestation in the current pregnancy, and not have known major fetal anomaly, maternal medical/obstetrical complications or a current or planned cerclage. Intramuscular injection of one ml of either 250 mg/ml 17OHP-C in vehicle (castor oil, benzyl benzoate and benzyl alcohol) or vehicle alone was administered weekly from randomization (16^0 and 20^6 weeks of gestation) through 36^6 weeks or delivery.

The primary efficacy endpoint was percent births <37 weeks gestation. Additional endpoints, requested by the FDA, included percent births <35 weeks and <32 weeks gestation, and a composite index of neonatal mortality and morbidity. The composite was based on the number of infants who experienced any one of the following: death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis or necrotizing enterocolitis (NEC).

3.4.2.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy endpoint in Study 17P-CT-002 was the proportion of preterm births occurring at <37 weeks gestation, analyzed using the intent to treat (ITT) population. Outcome data were available on all women (except four in the 17OHP-C group who were lost to follow-up) even if they withdrew from treatment prior to delivery. Results on this and secondary endpoints, as calculated by the FDA Statistical Reviewer, are displayed in Table 3. These results at <37 weeks continued to favor 17OHP-C when subgroup analyses categorized by gestational age of qualifying preterm birth, maternal race and number of previous preterm births were conducted.

Table 3 Efficacy Results – Study 17P-CT-002

Gestational Age [a]	17OHP-C[a] (N=310)	Vehicle (N=153)	Treatment difference [95% Confidence Interval, adjusted for interim analyses [b]]
	%	%	
$<37^0$ weeks	37.1	54.9	-17.8% [-28%, -7%]
$<35^0$ weeks	21.3	30.7	-9.4% [-18.7%, -0.2%]
$<32^0$ weeks	11.9	19.6	-7.7% [-16.1.%, -0.3%]
$<28^0$ weeks	9.4	10.5	-1.1% [-7.4%, 5.2%]

[a] Four 17P-treated patients were losses-to-follow-up. They are counted as deliveries at their gestational ages at time of last contact (18.6, 22.0, 34.4 and 36.6 weeks, respectively).
[b] To preserve the overall Type I error rate of 0.05, the adjusted confidence intervals (equivalent to a 96.6% confidence interval) use the final p-value boundary of 0.0345.

Source: FDA Statistical Review, Table 3.1

Team Leader Comments:

- ***There is a statistically significant treatment effect of 17OHP-C in preventing recurrent preterm birth at <37, <35 and <32 weeks.***

- ***The benefit of 17OHP-C appears to remain consistent over varying levels of risk, as measured by maternal race, number of prior preterm births and gestational age of qualifying preterm birth.***
- ***The rate of preterm birth <37 weeks in the placebo group is higher than that typically reported in trials in a similar population (e.g., other trials within the MFMU Network). The rate in the 17OHP-C group is more consistent with that typically seen in an untreated population.***

3.4.2.2 OTHER SECONDARY EFFICACY ANALYSES

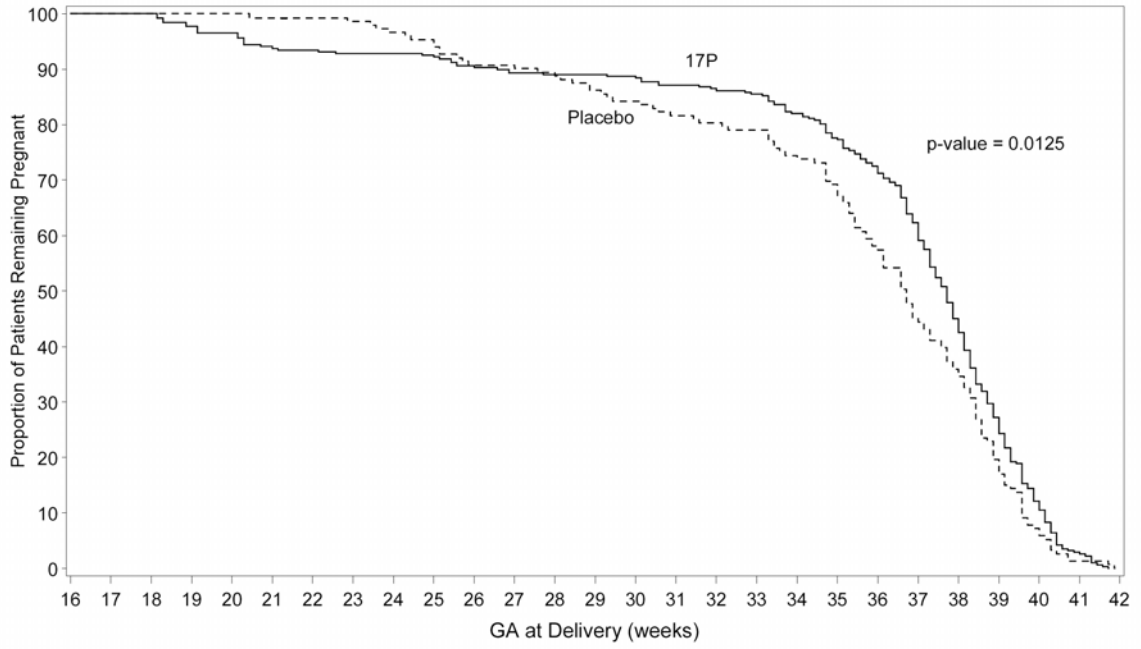
Following discussions with FDA, in which a preference for assessment of preterm birth at <35 and <32 weeks was expressed, post hoc analyses using these endpoints were conducted, and a statistically significant treatment effect of 17OHP-C was demonstrated (see Table 3). The Applicant also provided an assessment of the proportion of infants in each treatment arm with one or more events making up a composite endpoint of neonatal morbidity/mortality (comprising death, RDS, BPD, grade 3-4 IVH, sepsis or NEC). Although there was a lower proportion of subjects in the 17OHP-C group (11.9% vs. 17.2% in the vehicle group) who experienced at least one event of the composite endpoint, this difference was not statistically significant.

Team Leader Comment:

- ***The clinical trial was not powered to show a reduction in infant morbidity/mortality. The analysis of neonatal morbidity/mortality based on the composite endpoint was performed at the request of the Division.***

Pregnancy was maintained for an average of six days longer in the 17OHP-C group (131 vs. 125 days), with the mean gestational age at delivery being one week greater (36.2 vs. 35.2 weeks for 17OHP-C and vehicle subjects, respectively). The Applicant provided a Kaplan Meier analysis of the time to delivery in the two arms of the study, which showed a statistically significant difference in the shape of the curves by the log-rank test (see Figure 2).

Figure 2 Time to delivery as a function of gestational age, using staggered entry based on the gestational age at randomization – Study 17P-CT-002



Source: Applicant Response to FDA's request dated 7/20/06

Team Leader Comment:

- ***The Kaplan Meier curve demonstrates the prolongation of time to delivery in the 17OHP-C group starting at about 28 weeks. Prior to about 26 weeks, the 17OHP-C group has a higher rate of preterm delivery, attributable primarily to miscarriages and second trimester stillbirths.***

The frequency of tocolysis for preterm labor, cerclage placement and caesarian delivery were also evaluated. Rates of all three interventions were similar in both arms.

Team Leader Comment:

- ***If 17OHP-C were preventing preterm birth by acting on mechanisms that initiate premature labor, one would expect to see a reduction in the need for tocolytic agents in the 17OHP-C arm.***

The numbers of miscarriages, stillbirths, and neonatal deaths in each of the treatment groups are listed in Table 4. Five of 306 subjects assigned to the 17OHP-C group experienced miscarriages. No subject in the vehicle group miscarried. The incidence of stillbirths was slightly higher in the 17OHP-C group, but the difference was not statistically significant. Overall eight subjects had stillbirths: six (2.0%) subjects in the 17OHP-C group and two (1.3%) subjects in the vehicle group. The incidence of neonatal deaths was numerically twice as high in the vehicle group (6.0% vs. 2.7%, but the difference was not statistically significant. The overall incidence of fetal and neonatal mortality was similar in the two treatment groups ([6.2% in the 17OHP-C group and 7.2% in the vehicle group). Miscarriages, stillbirths, and neonatal deaths are discussed further in the Safety Section 3.5.1.

Table 4 Miscarriages, Stillbirths, and Neonatal Deaths - Study 17P-CT-002

Pregnancy Outcome	17OHP-C N=306 n (%) [A]	Vehicle N=153 n (%) [A]	Nominal P-value [B]
Miscarriages <20 weeks gestation	5 (2.4)[C]	0	0.17
Stillbirth	6 (2.0)	2 (1.3)	0.72
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.12
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.69**

[A] Percentages are based on number of enrolled subjects and not adjusted for time on drug.
[B] No adjustment for multiple comparisons.
[C] Adjusted for the number of at risk subjects (n=211) enrolled at <20 weeks gestation.
Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

Team Leader Comment:

- ***A similar relative increase in miscarriages and stillbirths was not observed in Study 17P-IF-001 (see Section 3.4.3.2)***

Additional endpoints evaluated neonatal outcomes, including the proportions with birthweight <2500 and <1500 g. The 17OHP-C arm had a statistically significantly lower percent of <2500 g infants (27% compared to 41% of vehicle-exposed neonates). The trend toward a lower proportion of <1500 g infants (8.6% in the 17OHP-C arm vs. 13.9% in the vehicle arm) was not statistically significant. Mean birthweight was numerically but not statistically greater in the 17OHP-C treatment group. There were no differences in mean 1 and 5 minute Apgar scores between offspring of 17OHP-C and vehicle treated women. Neonatal intensive care unit (NICU) admission, NICU stay and hospital stay were also compared; only NICU admission differed

significantly between groups, with 28% of 17OHP-C exposed infants admitted vs. 36% of vehicle-exposed infants. Individual components of the mortality/morbidity composite endpoint were also assessed, as were other outcome measures such as use of supplemental oxygen. Of 15 measures of neonatal morbidity evaluated, three were statistically significantly different, favoring a treatment effect for 17OHP-C: use of supplemental oxygen (15% vs. 24%), any IVH (1.4% vs. 5.3%) and NEC (0 vs. 2.7%).

Team Leader Comment:

- ***The analyses of individual neonatal morbidity endpoints were not adjusted for multiple comparisons and may not represent true treatment effects.***

3.4.3 Supportive Efficacy Study (Study 17P-IF-001)

Study 17P-IF-001 might be considered a supportive efficacy study, although of limited value due to early termination and questions about study drug potency. This trial was of the same design and used the same inclusion and exclusion criteria as Study 17P-CT-002.

3.4.3.1 PRIMARY EFFICACY ANALYSIS

The same primary efficacy endpoint, proportion of preterm births <37 weeks, was assessed in Study 17P-IF-001, for three population subsets: the ITT population, the total population for which data were available (exclusive only of subjects lost to follow-up) and the population of subjects whose treatment was not impacted by the recall of study drug (subjects who had either completed treatment or withdrawn from treatment prior to the recall). Results are shown in Table 5.

Table 5 Efficacy Results – Study 17P-IF-001

Analysis Population	17OHP-C		Vehicle	
	N	n (%)	N	n (%)
ITT population	94	39 (41.5)	56	20 (35.7)
All available data	93	38 (40.9)	54	18 (33.3)
Not withdrawn due to study termination	**65**	**28 (43.1)**	**39**	**15 (38.5)**

ITT population was all randomized subjects. Subjects with missing outcome data were classified as having a preterm birth $<37^0$ weeks (treatment failure).

Source: Table 9-3, pg 21, abbreviated Final Report for Study 17P-IF-001.

Team Leader Comment:

- ***There is no evidence of a treatment effect for 17OHP-C in this study, even in the population subset unaffected by study drug recall. However, questions about the drug potency limit the reliability of this finding.***
- ***Preterm birth rates in the vehicle-treated subsets are consistent with data from other MFMU Network studies, in contrast to the rate in Study 17P-CT-001.***

3.4.3.2 SECONDARY EFFICACY ANALYSIS

The combined fetal/neonatal death rate in the ITT population (Table 6) did not differ statistically between treatment arms (4.4% in the 17OHP-C arm and 5.9% in the vehicle arm).

Table 6 Miscarriages, Stillbirths, and Neonatal Deaths - Study 17P-IF-001

Fetal/Neonatal Deaths	17OHP-C N=93	Vehicle N=54
	n (%)	n (%)
Miscarriages	1 (1.1)	1 (1.9)
Stillbirths	1 (1.1)	2 (3.7)
Neonatal deaths	2 (2.2)	0
Total	**4 (4.4)**	**3 (5.9)**

Source: Table 9-8, pg 28, abbreviated Final Report for Study 17P-IF-001.

3.4.4 Additional Analyses Requested by FDA

Upon determination that the University of Alabama had contributed 27% of the sample size of Study 17P-CT-002, the Division requested that the Applicant provide a table analyzing the primary and key secondary endpoints for that single site, for all other sites and for all centers. Results are presented in Table 7.

Table 7 Percentages of Preterm Births at <37, <35, and <32 Weeks Gestation – Effect of Largest Center – Study 17P-CT-002

Gestation (weeks)	Percentage of Preterm Births								
	University of Alabama			All Other Centers Combined			All Centers		
	17OHP-C (n=86)	Vehicle (n=40)	Diff.	17OHP-C (n=224)	Vehicle (n=113)	Diff.	17OHP-C (n=310)	Vehicle (n=153)	Diff.
<37	26.7	45.0	-18.3	41.1	58.4	-17.3	37.1	54.9	-17.8
<35	17.4	27.5	-10.1	22.8	31.9	-9.1	21.3	30.7	-9.4
<32	10.5	25.0	-14.5	12.5	17.7	-5.2	11.9	19.6	-7.7

Source: Applicant's submission of October 10, 2006

Team Leader Comment:

- ***Although the rates of preterm birth at <37 and <35 weeks are lower in both arms of the University of Alabama sample than in all other centers, the difference in rate between 17OHP-C and vehicle arms are relatively consistent, suggesting a stable treatment effect across centers. The rates of preterm birth at <32 weeks diverge from the overall study trend, however, at the University of Alabama site – the preterm birth rate is higher in the vehicle arm and lower in the 17OHP-C arm than in all other centers combined, leading to a much higher treatment difference at <32 weeks at the Alabama site than in all other centers and in the study as a whole.***

The Applicant conducted several analyses to assess the possibility of a center effect, including an efficacy analysis with and without the University of Alabama site, a center by treatment interaction analysis using logistic regression, evaluation of consistency of treatment effect across centers using the Breslow-Day statistic and an adjusted analysis for center using the Cochrane-Mantel-Haensel statistic. The efficacy analysis with and without the University of Alabama produced results identical to the table above. The Applicant noted that the treatment differences at <32 weeks with (-7.7) and without (-5.2) the University of Alabama were similar, as were the relative risks of birth <32 weeks (0.68 with and 0.70 without the University of Alabama). The remaining analyses also indicated little likelihood that the effect at <32 weeks was being "driven" by this single center.

Team Leader Comment:

- ***Although the Applicant's analyses appear satisfactory, the large contribution to the total sample size by a single site is of concern in an application that is relying upon a single clinical trial to demonstrate efficacy. There are also exploratory analyses by the FDA Statistical Reviewer that suggest there may be an effect of the time of treatment initiation on efficacy: here again, disproportionate enrollment of women early in the eligibility window for gestational age at the University of Alabama may be impacting these results. These concerns further support my conclusion that a confirmatory trial is needed to evaluate whether the efficacy results are replicated in different centers.***

3.4.5 Overall Assessment of Efficacy

The Applicant attained statistical significance on the treatment difference in prevention of recurrent preterm birth at <37, <35 and <32 weeks in the primary study 17P-CT-002. There is minimal neonatal mortality or long-term morbidity seen among infants born between 35-37 weeks, and the Advisory Committee did not believe that delivery <37 weeks was an adequate surrogate for a reduced risk of fetal/neonatal mortality or neonatal morbidity (see Section 4). However, the endpoints of prevention of preterm birth at <35 and particularly <32 weeks were considered to be clinically meaningful, and were believed by the majority of the Advisory Committee members to be adequate surrogate measures.

Results were consistent across all centers at <37 and <35 weeks. At <32 weeks, however, there appears to be an interaction between center and treatment based on a much greater difference between treatment arms at the University of Alabama than is seen in the study as a whole or in all other centers combined. This suggests that the effect of 17OHP-C in prevention of preterm birth at <32 weeks may not be consistent across centers.

The Kaplan-Meier analysis of time to delivery demonstrated a statistically significant difference between "survival" curves for the two arms, reflecting both a prolongation of pregnancy in the 17OHP-C group from about 28 weeks of gestation on and an increased risk of preterm delivery from enrollment to about 26 weeks of gestation. The initial finding is reinforced by a statistically significant difference between treatment arms in prolongation of pregnancy and mean gestational age at delivery, favoring the 17OHP-C group.

Although there was a numerically lower rate of neonatal mortality in the 17OHP-C group, the increased frequency of early fetal loss in this group led to an overall finding of no difference in fetal/neonatal mortality by treatment group.

Other secondary outcome measures did not show a consistent pattern of statistically significantly differences between treatment arms. In particular, measures of neonatal outcome generally did not differ between treatment groups; however, the study was not powered to detect such differences.

3.5 SAFETY FINDINGS

As the NICHD trials were not originally conducted to support a marketing application for 17OHP-C, adverse events were not collected in the typical manner of studies designed to support drug approval. Adverse events considered by the investigator to be both serious and unexpected were assessed for severity and probable causality; non-serious adverse events were not assessed in this manner. Safety data from Study 17P-IF-001 was considered to be of limited value, since the potency of the test article was unknown. Safety findings discussed below pertain only to Study 17P-CT-001 unless otherwise specified.

3.5.1 Deaths and Serious Adverse Events

There were no maternal deaths in either Study 17P-IF-001 or Study 17P-CT-002.

Miscarriage and stillbirths occurred more frequently in the 17OHP-C group (3.5%) than in the vehicle group (1.3%) in Study 17P-CT-002, although the difference was not statistically significant (see Table 4). While there were no miscarriages in the vehicle group, five 17OHP-C-treated women miscarried (1.6%). Two of these women had clinical chorioamnionitis at the time of miscarriage; two had contributory factors (preterm premature rupture of membranes and cocaine use, respectively) and one had no identifiable risk factors, although she had been seen for a threatened abortion at 9 weeks gestation. The women had received between one and three injections at the time of miscarriage.

Team Leader Comments:

- ***While a higher rate of infection in the 17OHP-C group could result in an increased rate of miscarriage, the rate of chorioamnionitis and vaginitis in vehicle-treated women was not lower.***
- ***A meta-analysis of four published studies[4] also showed a possible association of 17OHP-C with miscarriage, demonstrating a nonsignificant odds ratio of 1.30 (95% confidence interval 0.61 to 2.74).***

Six stillbirths occurred in the 17OHP-C group (2%) as compared to two in the vehicle group (1.3%). One stillbirth in each group occurred intrapartum, with the remainder occurring as fetal deaths in utero. Infection may have been a contributing factor in four of the 17OHP-C and both of the vehicle stillbirths.

Team Leader Comment:

- ***As noted above, the rate of vaginal and intrauterine infections did not differ between the two treatment arms.***

Neonatal deaths occurred more often in the vehicle group (5.9% vs. 2.6% of the 17OHP-C group); this was also not statistically significantly different. Age at the time of death did not differ markedly between the treatment arms after excluding a 35 week neonatal death in the 17OHP-C group due to uterine rupture.

Team Leader Comments:

- ***The similar gestational ages at delivery of the infants who died in the neonatal period suggests that there would be little difference in the gestational age-adjusted neonatal death rate between the groups. It appears that the decreased neonatal death rate in the 17OHP-C arm is attributable to a lower proportion of early preterm deliveries as compared to the vehicle arm.***
- ***There was no difference in the overall fetal/neonatal death rate between the two arms; the reduction in neonatal death in the 17OHP-C group was offset by the increased rate of fetal loss. Thus, there is no net survival benefit to offspring of women treated with 17OHP-C.***
- ***Study 17P-IF-001 did not find an increased rate of miscarriage or stillbirth in the 17OHP-C arm (one miscarriage in each arm, two vehicle stillbirths and one 17OHP-C case) (see Table 6). Neonatal deaths occurred in two 17OHP-C subjects and one vehicle subject. The combined fetal/neonatal death rate in Study 17P-IF-001 did not differ statistically between treatment arms (4.4% in the 17OHP-C arm and 5.9% in the vehicle arm).***

Congenital anomalies were noted in 2% of each treatment group in Study 17P-CT-002, with a similar range of defects, including genitourinary and cardiovascular anomalies.

Team Leader Comment:

- ***The general population background rate for congenital anomalies is 2-3%.***

Serious unexpected non-fatal adverse events occurred in three women and one infant exposed to 17OHP-C. These included a postpartum pulmonary embolus, cellulitis at the injection site after the 8th injection, postpartum hemorrhage and respiratory distress after a 21 week stillbirth and a male infant delivered at 37^5 weeks with infarcted testicles secondary to intrauterine torsion.

Team Leader Comment:

- ***I agree with Dr. Wesley that these SAEs are unlikely to be causally related to 17OHP-C.***

3.5.2 Other Adverse Events

Discontinuation due to adverse events occurred in seven 17OHP-C subjects and four vehicle subjects. Urticaria and injection site pain were the most common reasons for discontinuation. The most common adverse events in the 17OHP-C and vehicle groups, respectively, were injection site pain (35% and 33%), injection site swelling (17% and 8%), urticaria (12% and 11%), pruritis (8%, in 17OHP-C group only), injection site pruritis (6% each), nausea (6%, in 17OHP-C group only), contusion (6% and 9%), and neonatal death (6%, in vehicle group only).

Maternal complications were reported in both Studies 17P-CT-002 and 17P-IF-001. The proportion of women with three relatively common pregnancy complications (gestational diabetes, oligohydramnios and preeclampsia) was greater in both studies in the 17OHP-C arm as compared to the vehicle arm (see Table 8).

Table 8 Selected Pregnancy Complications: Studies 17P-CT-002 and 17P-IF-001

Pregnancy Complication	Study	17OHP-C N	17OHP-C (%)	Vehicle N	Vehicle (%)
Gestational Diabetes	CT- 002	17	(5.6)	7	(4.6)
	IF- 001	8	(8.6)	0	(0.0)
Oligohydramnios	CT- 002	11	(3.6)	2	(1.3)
	IF- 001	2	(2.2)	1	(1.9)
Preeclampsia	CT- 002	27	(8.8)	7	(4.6)
	IF- 001	6	(6.5)	2	(3.8)

Source: Primary Medical Review, p 57, adapted from table 12-3 Final Report for Study 17-CT-002

Team Leader Comment:

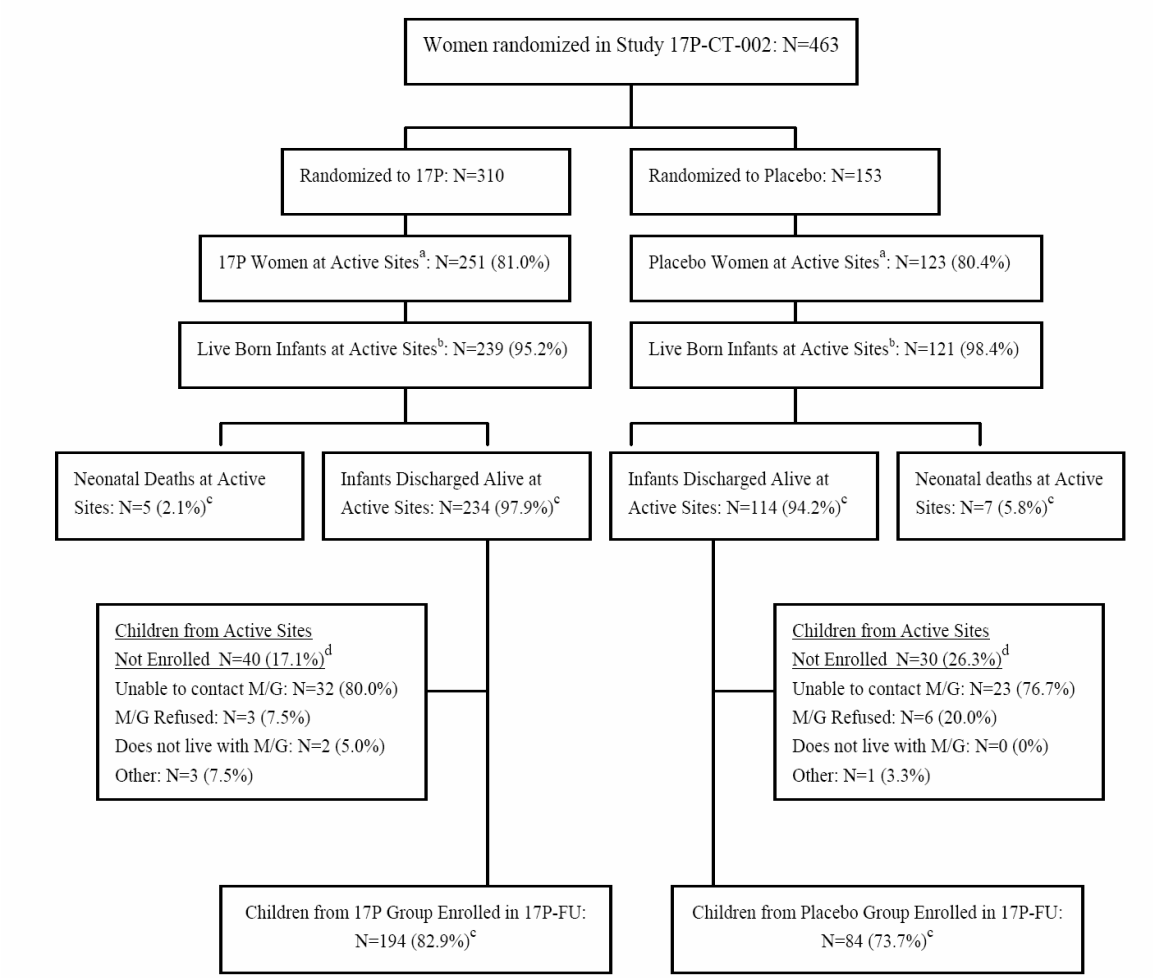
- ***All three of these complications are identified more frequently as pregnancy advances; therefore the apparent increased rates may be attributable to the prolongation of pregnancy in the 17OHP-C arm, rather than to an adverse effect of the drug.***

3.5.3 Infant Follow-up Study

Study 17P-FU was conducted at the Division's request, to provide outcome data on the children born to women treated in Study 17P-CT-002 at two years of age or greater. In this study, of the 463 women randomized in Study 17P-CT-002, 374 were enrolled in sites remaining active in the MFMU Network at the time of the follow-up study. Disposition of subjects in this study is shown in Figure 3. Of 348 eligible children, 278 (80%) enrolled in Study 17P-FU (83% of

17OHP-C-exposed children and 74% of vehicle-exposed children). Age at enrollment ranged from 30 to 64 months.

Figure 3 Subject Disposition – Study 17P-FU



Abbreviations: M/G = mother/guardian

[a] An active study site was a clinical center participating in the MFMU Network at the time Study 17P-FU was conducted.

[b] Percentages were based on the number of patients from active study sites.

[c] Percentages were based on the number of live born infants in Study 17P-CT-002 from active study sites.

[d] Percentages were based on the number of live born infants in Study 17P-CT-002 discharged from birth hospitalization from active study sites.

Source: Section 10.1, Figure 10-1, Final Report for Study 17P-FU.

Team Leader Comment:

- ***The Applicant provided follow-up data on more than the 35-50% of the children that the FDA had specified as the minimal acceptable proportion of follow-up. The children followed were all at least 2.5 years of age, ranging up to 5 years of age.***
- ***The mean gestational ages of the children in Study 17P-FU were one week greater than those seen in the total cohort of 17OHP-C and vehicle-exposed children in Study 17P-CT-002. They may therefore represent a slightly lower risk group than the original population.***

There were no deaths in either group following discharge from the birth hospitalization.

The follow-up study collected data with a validated child development instrument, the Ages and Stages Questionnaire (ASQ), a Survey Questionnaire concerning the health and development of the child, and a physical examination. The ASQ evaluates communication, gross and fine motor, problem solving and personal-social skills. The Survey Questionnaire evaluated overall activity level and motor control, vision/hearing problems, growth (height, weight and head circumference), gender-specific behavior and reported diagnosis by a healthcare provider of various sensory and neurodevelopmental disorders, asthma, and allergies. The children were at least two years of age at the time of the follow-up assessments. The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received weekly intramuscular injections of 17OHP-C compared with placebo during the pregnancy in Study 17P-CT-002.

There were no differences between the two arms in the percent of children who scored below the cutoff (≥2 standard deviations below the mean) used to identify potential cases of developmental delay on the ASQ (27.5% in 17OHP-C vs. 28.0% in the vehicle group).

Team Leader Comment:

- ***The rate of ASQ scores below the cutoff, signifying possible developmental delay, was higher in this study than would be expected based on normative data for the instrument. As vehicle-exposed children had a greater frequency of very low birthweight (<1500 gm) and delivery prior to 32 weeks, it would be expected that a higher proportion of vehicle-exposed children would be at risk for developmental delays on the basis of these perinatal risk factors. The classification of equal proportions (about 28%) of children in each group as possibly delayed suggests that the 17OHP-C group also resembled an "at risk" group, albeit not as strongly attributable to low birthweight and gestational age. The Applicant did not conduct an analysis adjusting for these risk factors in assessing the proportion of possibly delayed children in each treatment group.***

Children who scored below cutoff on at least one item on the ASQ who also had an independent diagnosis of developmental delay made by a professional prior to the follow-up period (as reported by the parent) were considered to represent "true positives" on the ASQ screen. This occurred in 6.7% of 17OHP-C exposed children and 9.8% of vehicle-exposed children. The specific developmental areas falling below the ASQ cutoff for these children are shown in Table 9.

Table 9 Development Delay in Children from Study 17P-CT-002

ASQ Area of Development below Cutoff	17OHP-C n = 13	Vehicle n = 8
	Percent Affected	
Communication	4.7	8.5
Gross motor	1.6	2.4
Fine motor	5.2	3.6
Problem solving	2.6	6.1
Personal-social	2.6	1.2

Team Leader Comment:

- ***Based on this small number of children and the other assessments, there is no suggestion of adverse effects on postnatal development in the children whose mothers had been treated with 17OHP-C during their pregnancy. There is also no indication that maternal treatment with 17OHP-C resulted in any beneficial effect***

on early childhood development despite the prolongation of pregnancy and decrease in the rate of preterm birth; however, the study was not powered to detect such an effect.

The two groups of children had similar results on the Survey Questionnaire. Fewer than 5% of 17OHP-C exposed children had any reported impairments or diagnoses of developmental disorders, with the most frequent reports being communication problems (4.7%) and inability to pay attention/learn (4.2%). In the vehicle-exposed children, 8.5% were reported to have been diagnosed with communication problems and 6.1% each with inability to pay attention/learn, hearing impairment and impairment in ability to walk/run/play.

Team Leader Comment:

- ***A neurological examination was not performed during the follow-up physical exam.***

Genital or reproductive abnormalities were assessed by parental report on the Survey Questionnaire and during the follow-up physical examination. Four children (2.1%) of children exposed to 17OHP-C and one (1.2%) exposed to vehicle were noted to have such abnormalities, including micropenis (2), undescended testes and early puberty in the 17OHP-C group and "sparse pubic hair" in a 42 month old girl in the vehicle group.

Study 17P-FU was reviewed by (b) (4) at the Division's request. She noted strengths of the study to include:

- Use of the ASQ as the screening instrument; this is an excellent screening tool with good validity for developmental delays
- Obtaining follow-up data on 80% of available subjects
- The data collection and verification appear to have been of high quality

Study weaknesses, in her opinion, include:

- The data were primarily dependent on parental report
- The Survey Questionnaire relied on parent report of a health provider telling them of certain diagnoses including developmental delay. It is possible that even if a pediatrician had noted a delay, he/she may not have used that terminology or sufficiently explained it to a parent.
- The ASQ is meant to be combined with other strategies as part of a comprehensive follow-up of at-risk infants. It would have strengthened this study if those children who failed the screening ASQ were then formally evaluated by an age-appropriate standard psychometric test."
- The rate of ASQ score below the cutoff was higher in both groups (28%) than expected (2.5 to 12%). It would have been helpful to have included a comparison group of term infants matched for ethnic and socioeconomic characteristics to the study group.
- There is no evidence that a neurologic exam was performed as part of the assessments. The physical exam form does not include assessment of muscle tone, deep tendon reflexes, dexterity, gait, or balance.
- Due to the change in centers in the MFMU Network, children from five centers were not assessed. Therefore only 65% of live born children exposed to study drug or placebo *in utero* were evaluated for this follow-up assessment.
- The contribution of center to the outcomes was not analyzed. One center, U. Alabama at Birmingham contributed 30% of the placebo and 35% of 17P subjects with much smaller contributions from the other 13 sites.

- Although the objective of the follow-up study was to assess long term safety of 17OHP –C and not efficacy, it would be reasonable to expect that a lower rate of preterm birth would improve neurodevelopmental outcome compared to placebo. The original sample size was not powered to address this outcome, but interventions to prevent preterm births that do not impact on the long term outcomes of children born to mothers at risk will not affect the major cost of preterm birth (i.e. life long disabilities, medical morbidities).

3.5.4 Overall Assessment of Safety Findings

There is a signal of possible increased fetal loss in Study 17P-CT-002, consisting of higher rates of miscarriage and second trimester stillbirths in women treated with 17OHP-C. This finding was not seen in Study 17P-IF-001; however, it has been noted in a published meta-analysis[4]. The higher rate of early fetal loss resulted in no survival advantage in the 17OHP-C group, despite having a lower neonatal death rate.

The rate of congenital anomalies in both groups was consistent with background rates in the general population.

There were no maternal deaths or SAEs likely to be causally related to 17OHP-C. The rate of discontinuation due to adverse events was <3% in both groups. Common adverse events typically involved injection site reactions, pruritis and urticaria, seen in both groups.

Women treated with 17OHP-C did have slightly higher frequency of gestational diabetes, oligohydramnios and preeclampsia, in both Studies 17P-CT-002 and 17P-IF-001. It is unknown whether this is attributable to the longer duration of pregnancy in women receiving 17OHP-C.

Regarding Study 17P-IF, the follow-up study evaluated a reasonable proportion of children exposed to 17OHP-C or vehicle prenatally. As noted previously, both the 17OHP-C and vehicle treated children in the follow-up study may represent a slightly lower risk subset of the total population children of mothers who participated in study 17P-CT-002, given their greater mean gestational age as compared to the total cohort of children from study 7P-CT-002.

There was no difference between the 17OHP-C and vehicle groups in the percentage of children who scored below the cutoff for at least one developmental area of the ASQ. The percentages of children who scored below the ASQ cutoff in each of the individual five developmental areas also were similar in the 17OHP-C and vehicle groups.

Developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age mates in physical, mental, social/emotional, or speech development, was reported for a comparable percentage of children in the 17OHP-C and vehicle groups.

Overall, there is no evidence of either harm or benefit on the development of children born to pregnancies treated with 17OHP-C.

3.6 RISK/BENEFIT ANALYSIS OF 17OHP-C FOR PREVENTION OF RECURRENT PRETERM BIRTH

The public health importance of preterm birth and the lack of efficacious treatment of preterm labor must be considered in weighing the risk/benefit ratio for a drug proposed for the indication of prevention of recurrent preterm birth. The fact that 17OHP-C is being compounded and used widely, with no regulatory oversight or monitoring of adverse events, is also a consideration.

However, it does not appear that the primary trial meets the general requirements for acceptance of a single adequate and well-controlled trial to establish efficacy of a drug. The clinical trial data

did not provide evidence of a clinically meaningful or statistically significant effect on neonatal morbidity or mortality, as measured by a composite endpoint. However, preterm birth can be considered "a disease with potentially serious outcome," as discussed in the FDA Guidance, and the trial did succeed in demonstrating efficacy of 17OHP-C in preventing preterm birth at <35 and <32 weeks of gestation, cutpoints which the majority of members of the Advisory Committee on Reproductive Health Drugs believed represented adequate surrogates for fetal/neonatal mortality and neonatal morbidity. There remains a question as to whether the benefit of 17OHP-C in prevention of preterm birth at <32 weeks in Study 17P-CT-002 is largely attributable to a single study site, or whether this result generalizes.

In addition, the clinical data suggest that there may be safety issues, particularly involving increased early fetal loss in women treated with 17OHP-C, a finding that mirrors nonclinical data relating high doses of 17OHP-C with increased embryolethality in mice, rats and monkeys. The majority of the Advisory Committee believed it was acceptable for this to be studied post-approval.

Therefore, I conclude that, while the Applicant has demonstrated efficacy of 17OHP-C in a single trial in reducing the risk of preterm birth at gestational ages that correlate with increased neonatal morbidity and mortality, these data are not sufficiently robust to support approval at this time. At a minimum, it needs to be determined whether a randomized, controlled confirmatory trial could be undertaken. Even if a placebo-controlled trial were not feasible, further study to determine the long-term safety of prenatal exposure to 17OHP-C, as well as to elucidate the signal of possible increased fetal mortality, is necessary.

4 ADVISORY COMMITTEE RECOMMENDATIONS

NDA 21-945 was presented before the Advisory Committee on Reproductive Health Drugs on August 29, 2006. A majority of committee members voted that prevention of preterm birth <35 weeks was an adequate surrogate for a reduction in fetal/neonatal mortality and neonatal morbidity; the vote was nearly unanimous that prevention of preterm birth <32 weeks was an adequate surrogate. Few committee members found prevention of preterm birth <37 weeks to be an adequate surrogate. A majority of members voted that the data submitted provide substantial evidence that 17OHP-C prevents preterm birth at <35 weeks; a majority felt that there was not substantial evidence for effectiveness at <32 weeks. The committee voted unanimously that further study is needed to evaluate the potential association of 17OHP-C with second trimester miscarriage/stillbirth; the majority believed that this could be studied post-approval. The committee also voted unanimously that a post-approval clinical trial or trials be conducted for further investigation of safety and effectiveness. Issues to be addressed in such a mandatory post-approval study include evaluation of the possible increased risk of miscarriage/stillbirth, assessment of possible maternal complications, and elucidation of PK and pharmacodynamic properties of 17OHP-C. In addition, long-term follow-up (including reproductive development/function, fertility and carcinogenic potential of 17OHP-C) will need to be obtained in a subsequent study or perhaps through use of a registry.

Team Leader Comment:

- ***The data presented to the Advisory Committee for the rate of preterm birth at <32 weeks did not demonstrate statistical significance. However, subsequent review and analysis by the FDA Statistical Reviewer has confirmed that the treatment effect of 17OHP-C at <32 weeks is statistically significant.***

5 LABELING ISSUES

Labeling discussions were deferred to the next review cycle.

6 RECOMMENDATIONS OF OTHER DISCIPLINES AND DIVISIONS

6.1 TOXICOLOGY AND PRECLINICAL PHARMACOLOGY

The primary Toxicology Reviewer, Wafa Harrouk, Ph.D., made the following recommendations in her review dated September 21, 2006:

Recommendations on approvability: *Approvable*

Recommendations for nonclinical studies: *A state of the art, GLP-compliant, multigenerational reproductive toxicology study which covers the stages of pregnancy covered in the clinic, is recommended to evaluate the safety of 17-HPC [17-alpha-hydroxyprogesterone caproate] on maternal and fetal health.*

Recommendations on labeling: *Although no teratogenicity was seen in mice of monkeys (Rhesus and Cynomolgus), it should be stated that fetal deaths were seen in the Rhesus reproductive toxicity study. No well-controlled nonclinical toxicity studies have been conducted with 17-HPC to support the indication of preterm labor.*

The Pharmacology/Toxicology Team Leader, Lynnda Reid, concluded in her memorandum dated September 21, 2006:

- **From a Pharmacology/Toxicology standpoint, this NDA is approvable. There is insufficient nonclinical data on which to base the safety of 17-HPC, especially in regards to long-term effects in offspring exposed in utero. We recommend that a thorough reproductive and developmental study be performed in accordance with ICH S5A "Guideline for Industry: Detection of Toxicity to Reproduction for Medicinal Products." A multigenerational study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including learning, behavior and reproductive function, in offspring exposed in utero.**

6.2 CMC AND PRODUCT MICROBIOLOGY

The primary Chemistry Reviewer, Monica Cooper, Ph.D., made the following recommendations in her review dated September 22, 2006:

This new drug application (21-945) is ***APPROVABLE*** *from the perspective of chemistry, manufacturing and controls. Issues regarding drug product photosensitivity and particulate matter, which impact the storage and expiration date for the drug product, remain unresolved.*

The Office of Compliance has given an overall acceptable recommendation for the manufacturing and testing facilities.

Labeling issues will be addressed during the second review cycle.

A number of deficiencies regarding photostability and expiry, to be outlined in the action letter, were listed. No phase 4 commitments were requested.

6.3 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The primary Clinical Pharmacology and Biopharmaceutics Reviewer, Doahn Tran, Ph.D., stated the following in his review dated September 21, 2006:

This reviewer finds NDA 21-945 acceptable from a clinical pharmacology perspective provided the labeling comments are adequately addressed.

In the event that there are additional clinical trials planned or requested the following pharmacokinetic [PK] elements are recommended to be included as part of those trials to allow for better understanding of the 17-HPC pharmacokinetics and optimal dosing:

1. *Characterize the pharmacokinetics of 17-alpha-hydroxyprogesterone (17-OHP), 17-HPC and its metabolites in pregnant women (includes both plasma and urine concentrations) at several periods throughout the pregnancy.*
2. *Assess the 17-HPC exposure response relationship and the effect of body weight on the pharmacokinetics of 17-HPC via sparse sampling of all subjects.*
3. *Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on 17-HPC PK.*

6.4 MICROBIOLOGY

The Microbiology Reviewer, John Metcalfe, Ph.D., made the following recommendation in his review dated August 9, 2006:

NDA 21-945 is recommended for approval from the standpoint of product quality microbiology.

No phase 4 commitments were recommended.

6.5 STATISTICS

The Statistical Reviewer, Lisa Kammerman, Ph.D., included the following statements in the "Conclusions and Recommendations" of her review dated October 19, 2006:

From a statistical perspective, the level of evidence from Study 17P-CT002 is not sufficient to support the effectiveness of 17P. The primary reason is the absence of a second, confirmatory study. Without a second study, the generalizability of the study results to a larger population cannot be assessed.

Study 17P-CT002 was stopped after the second interim analysis, which showed that Delivery <37 weeks gestation had met the stopping rules in favor of 17P. Subsequently, analyses showed that Delivery prior to 35 weeks gestation and delivery prior to 32 weeks gestation were statistically significant when accounting for the interim analyses. Although the results are statistically significant for 35 weeks and 32 weeks when accounting for interim analyses, the confidence intervals for the treatment effects are not convincing when considering that only one study was submitted to support the claim of effectiveness for 17P.

The "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" sets forth guidance needed for the FDA to accept results from a single, clinical study. Using the guidance document, I focused my review on whether the results could be generalized to a larger population, or not. The guidance on clinical evidence stresses the importance of a large multi-center study to help establish the credibility of a single study submission and that the credibility is enhanced if no single center accounts for an unusually large proportion of the subjects.

When compared with all other centers, one center, the University of Alabama, is disproportionately represented in the study. The University of Alabama accounts for about 25% of all subjects enrolled (126/463) and is about three times the size of the next largest center, the University of Tennessee (45/463 = 9.7%).

The effect of 17P is most pronounced when started at 18 weeks gestation or earlier and does not appear effective when started at 20 weeks of gestation or later. The rate of fetal and neonatal deaths is also most pronounced among women who started study drug at 18 weeks

gestation or earlier (10%). The rate decreases to 2% when study drug is started at 20 weeks of gestation or later. The results of my analyses suggest the presence of confounding between center and gestational age at randomization. For example, the University of Alabama accounts for 44% of subjects enrolled at 18 weeks gestation or earlier and had relatively few patients at later ages. At other centers, the gestational age at randomization is skewed towards later gestational ages at the time of randomization.

When two studies are submitted, the chance of both studies yielding a false positive result is 1/1600. In the case of a single study, the results must be less than a nominal p-value of 0.00125 to ensure the same false positive rate. In Study 17P-CT-002, the only endpoint that meets this criterion is Delivery <37 weeks gestation. Deliveries at times earlier than 37 weeks gestation were not statistically significant at 0.001. The results of the analyses of the 32 and 35 week endpoints suggest their false positive rates could be as great as 1/40.

Because of the public health need for a drug product to prevent preterm deliveries, we might be willing to accept a false positive rate that is somewhat greater than 1/1600 if the results appear to be generalizable. However, because of the issues introduced by the size of the University of Alabama and its findings, together with the 1/40 false positive rates for the 32 and 35 week endpoints, I do not believe the study results can be generalized to a larger population.

Therefore, from a statistical perspective, I do not believe this study meets the level of evidence needed to support the efficacy of 17P.

Team Leader Comments:

- ***The recommended level of significance could also be achieved by conducting a confirmatory study. This should be addressed by exploring the feasibility of such a study that could be conducted as a component of approval under Subpart H.***
- ***The suggestion that efficacy of 17OHP-C may be moderated by the timing of initiation of treatment is based upon an exploratory, post hoc analysis. It would be appropriate to investigate this further, in a prespecified analysis, in a confirmatory study.***

6.6 DIVISION OF SCIENTIFIC INVESTIGATION

The Division of Scientific Investigation (DSI) planned to inspect three sites for NDA 21-945 (University of Alabama, University of Tennessee and University of Utah), chosen based upon their having the largest enrollment of the 19 participating sites. At the time of this review, only the University of Alabama inspection report had been completed. Roy Blay, Ph.D. from DSI made the following overall assessment in his review of this site's inspection report, dated August 16, 2006:

The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the respective indication.

The remaining two site inspections/reports will be completed after the present action is taken.

6.7 OFFICE OF DRUG SAFETY/DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT

Felicia Duffy, RN, of the Division of Medication Errors and Technical Support (DMETS) made the following recommendations in her review dated September 13, 2006:

1. *DMETS does not recommend the use of the proprietary name, Gestiva.*
2. *DMETS recommends implementation of the label and labeling revisions outlined…in order to minimize potential errors with the use of this product.*

3. *DDMAC has no objections to the proposed name, Gestiva, from a promotional perspective. However, DDMAC has the following comment:*

Team Leader Comment:

- ***The Applicant has been informed of these concerns. No decision regarding a final Trade name has been made.***

6.8 OFFICE OF DRUG SAFETY/DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS

Corrinne Kulick of the Division of Drug Marketing, Advertising and Communications (DDMAC) made a number of recommendations about labeling. These will be addressed in the next review cycle.

6.9 OFFICE OF DRUG SAFETY/ DIVISION OF DRUG RESEARCH AND EVALUATION

Adrienne Rothstein, Pharm.D., of the Division of Drug Research and Evaluation (DDRE) was consulted to review the Adverse Events Reporting System (AERS) database for all adverse event reports submitted since June 2003 (coinciding with the publication of the NICHD trial in the New England Journal of Medicine). After reviewing the four reports entered in the AERS database, she reached the following conclusion in her review dated August 22, 2006:

> *These few reports of early gestational exposure are of limited value to an assessment of 17α-hydroxyprogesterone caproate for the prevention of recurrent pre-term birth.*
>
> *Thus, no conclusions can be made at this point in time from the limited number of reports in AERS for 17α-hydroxyprogesterone caproate.*

---

[1] Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998, p3

[2] ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 291, November 2003

[3] Meis PJ et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 348: 2379-85, 2003.

[4] Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Brit J Obstet Gynecol 97: 149-54, 1990

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/s/

Jennifer L. Mercier
10/20/2006 08:54:39 AM
CSO

Ronald Orleans
10/20/2006 09:00:14 AM
MEDICAL OFFICER
Acting Team Leader signing for Dr. Lisa Soule

Scott Monroe
10/20/2006 09:26:48 AM
MEDICAL OFFICER
I concur with the conclusions of Dr. Soule and
her recommendation that NDA 21-945 (17-hydroxyprogesterone caproate) receiv
an approvable action for prevention of preterm birth
in women with a history of at least
one spontaneous preterm birth.

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-945
Submission Code	P
Letter Date	14 April 2006
Stamp Date	20 April 2006
PDUFA Goal Date	October 20, 2006
Reviewer Name	Barbara Wesley, M.D., M.P.H.
Review Completion Date	October 18, 2006
Established Name	17 alpha hydroxyprogesterone caproate injectable
Trade Name	Gestiva (proposed)
Therapeutic Class	Progestogen
Applicant	Adeza Biomedical
Priority Designation	P
Formulation	Injectable (IM)
Dosing Regimen	250 mg (1 mL) weekly from between 16 weeks 0 days and 20 weeks 6 days to 37 weeks of gestation or until birth
Indication	Prevention of preterm birth
Intended Population	Pregnant women with a history of at least one spontaneous preterm birth

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends an approvable action for Gestiva [17α-hydroxyprogesterone caproate or 17OHP-C)] for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth. This recommendation is based on one multicenter clinical trial showing statistically significant reductions in preterm birth (PTB) at <35 and < 32 weeks gestation, surrogate endpoints recommended by an Advisory committee to predict reduction in neonatal mortality and morbidity. Additionally, although previous studies are small, the data from the literature consistently demonstrates a decrease in PTB when women with a previous PTB or miscarriage are treated with 17OHP-C.

Approval is contingent on the following:

- Reassuring data from a multi-generational reproductive toxicology study for 17OHP-C..

Approval is also contingent on the following as a post approval commitment

- Safety studies to assess to potential association of 17OHP-C with miscarriages/ stillbirths, and long term safety evaluations of children at age 18-24 months and during adolescence.
- Additional data to provide further statistical support for the effectiveness of 17OHP-C to reduce the incidence of preterm birth (PTB) particularly at <35 and <32 weeks gestational age.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management actions are recommended at this time.

1.2.2 Required Phase 4 Commitments

Further study is needed to evaluate the following potential safety issues with 17OHP-C:

- The potential association of 17OHP-C with increased risk of second trimester miscarriage and stillbirth.
- Additional assessment of children at age 18-24 months whose mothers were treated with 17OHP-C including a screening assessment, and a formal psychometric assessment for those who screen positive, with an assessment by a neurologist.
- Long-term safety data from children (at least through puberty) whose mothers were treated with 17OHP-C, with a particular emphasis on the status of the reproductive system. These data can best be obtained through establishment of a surveillance program (e.g. a registry) to evaluate exposure effects in adolescents.

The Applicant will need to obtain more data to provide additional statistical support for the effectiveness of 17OHP-C to reduce the incidence of preterm birth (PTB) particularly at <35 and <32 weeks gestational age. Ideally, the study would also provide statistical support for the effectiveness of 17OHP-C to reduce morbidity and possibly mortality associated with PTB. The

Division recognizes the challenges of such a study, particularly the use of a placebo arm. The Applicant should discuss with potential investigators, either individually or in small groups, potential study designs that would provide further evidence of effectiveness of 17OHP-C. The content of these discussions should be fully documented, particularly whether investigators would be willing to participate in a clinical trial that included a placebo arm. These discussions should be conducted with investigators within the Maternal-Fetal Medicine Network Units sites and with investigators who are not within this network. If a clinical trial with a placebo arm is not feasible, based on discussions with potential investigators, the Applicant will need to explore the feasibility of other adequate and well-controlled clinical trial designs that could provide statistically significant information supporting the effectiveness of 17OHP-C in reducing the incidence of PTB at <35 and <32 weeks gestational age.

1.2.3 Other Phase 4 Requests

In consultation with the clinical pharmacologist (Dr. Tran), the following studies are requested as part of a postmarketing commitment (see clinical pharmacology review):

1. Characterize the pharmacokinetics of 17OHP-C and its metabolites in pregnant women (includes both plasma and urine concentrations) at several periods throughout the pregnancy. Assess the 17OHP-C exposure response relationship via sparse sampling of all subjects.
2. Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on 17OHP-C pharmacokinetics.
3. Assess the effect of body weight on the pharmacokinetics of 17OHP-C using samplings specified in comment 2.
4. Examine the effect of hepatic impairment on 17OHP-C pharmacokinetics.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In support of their application for the use of 17OHP-C for the prevention of preterm birth, the Applicant submitted data from two active treatment clinical trials (study 17P-IF-001 and study 17P-CT-002) and a follow-up safety study (study 17P-FU).

Initial Formulation Study (Study 17P-IF-001). This study began in February 1998, but treatment was terminated in March 1999 because the active study drug (17OHP-C) was recalled by its manufacturer, under the direction of the FDA, due to violations of manufacturing practices potentially affecting the potency of the drug. At the time of termination, only 150 of the proposed 500 subjects had been randomized, and no data analysis had been done. Eighty six (86) subjects completed the treatment regimen before the study was stopped: 57 of the 17OHP-C subjects and 29 of the vehicle subjects. The study drug used in this prematurely terminated study is referred to as the Initial Formulation (IF). Information from this study was considered to be of limited value in supporting either the safety or efficacy of 17OHP-C and are not discussed further in this section of the review.

Principal Safety and Efficacy Trial (Study 17P-CT-002). The principal study was a double blind, vehicle controlled trial, that randomized subjects 2:1 to 17OHP-C or vehicle. Inclusion criteria were pregnant women with a history of a previous spontaneous singleton preterm birth, who were at a gestational age between 16 weeks-0 days (16^0) and 20 weeks-6 days (20^6) at randomization. The main exclusion criteria included a known major anomaly, prior progesterone or heparin treatment in the current pregnancy, a history of thromboembolic disease and maternal medical/obstetrical complications, hypertension requiring medication, or a seizure disorder. Study medications were 17OHP-C (250 mg/mL) in castor oil or vehicle. The dosing regime was a 250 mg weekly injection of 17OHP-C, or 1 mL vehicle, beginning on the day of randomization through 36^6 weeks gestation, or delivery, which ever occurred first.

The primary efficacy endpoint was percent births <37 weeks gestation. Additional endpoints, requested by the FDA, included percent births <35 weeks and <32 weeks gestation, and a composite index of neonatal morbidity. The composite was based on the number of infants who experienced any one of the following: death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis or necrotizing enterocolitis (NEC). This study was designed to enroll 500 subjects; however, because the prespecified stopping criterion for efficacy was attained at an interim analysis, only 463 subjects were randomized (2:1 to 17OHP-C vs. vehicle) and treated with study medication: 310 in the 17OHP-C arm and 153 in the vehicle arm. Twenty seven (27) subjects withdrew from treatment in the 17OHP-C arm vs. 14 in the vehicle arm, but remained in the study. In the 17OHP-C arm, 6 withdrew due to an adverse event, compared to 3 in the vehicle arm. Four subjects were lost to follow-up, all in the 17OHP-C arm.

Follow-up Safety Study (Study 17P-FU). This was a safety study of children whose mothers had participated in Study 17P-CT-002. The study collected data with a validated child development instrument (the Ages and Stages Questionnaire [ASQ]), a Survey Questionnaire concerning the health and development of the child, and a physical examination. All children were at least 2 years of age at the time of the follow-up assessments. The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received weekly intramuscular injections of 17OHP-C compared with vehicle in Study 17P-CT-002. Two hundred seventy eight (278) children were enrolled: 194 from the 17OHP-C arm, and 84 from the vehicle arm of Study 17P-CT-002.

1.3.2 Efficacy

Study 17P-CT-002. The primary efficacy endpoint was the percent of preterm births (PTBs) <37 weeks gestation and the analysis was based on the intent-to-treat (ITT) population, all subjects who received study medication (see Table A). Of the 310 subjects treated with 17OHP-C, 115 (37.1%) delivered prematurely. Of the 153 subjects treated with vehicle, 84 (54.9%) delivered prematurely. There was a 17.8% reduction (95% CI:-28%, -7%) in preterm births <37 weeks gestation. The reduction in preterm birth < 37 weeks was independent of race, number of qualifying preterm births, and gestational age of the qualifying preterm birth. The percentages of PTBs in the 17OHP arm at <35 and <32 weeks were also statistically lower than those in the vehicle arm. The point estimates of the differences were -9.4% (95% CI:-18.7%, -0,2%) at <35 weeks and -7.7% (95% CI:-16.1%, -0.3%) at <32 weeks.

Table A. Proportion (95% Confidence Interval) of Subjects with Delivery at <37^0, <35^0, <32^0, and <28^0 Weeks Gestational age (FDA Analysis).

Data Source	17OHP-C (N=310)	Vehicle (N=153)	Mean Treatment Differences and 95% Confidence Interval [A]
	%	%	
<37^0 weeks	37.1	54.9	-17.8% [-28%, -7%]
<35^0 weeks	21.3	30.7	-9.4% [-18.7%, -0.2%]
<32^0 weeks	11.9	19.6	-7.7% [-16.1.%, -0.3%]
<28^0 weeks	9.4	10.5	-1.1% [-7.4%, 5.2%]

[A] The confidence intervals have been adjusted for the 2 interim analyses and the final analysis to preserve the overall Type I error rate of 0.05,

There was consistency in the reduction of PTBs across centers at < 37 weeks and < 35 weeks gestation; however, at < 32 weeks there was a greater reduction of PTB in the 17OHP-C arm relative to vehicle at the University of Alabama compared to all other sites combined.

The number of infants with a birthweight < 2500 g, corresponding to ≤ 37 weeks gestational age, was statistically lower in the 17OHP-C arm (27.2% , 82/301) vs. 41.1% (62/151) in the vehicle arm. The number with a birthweight < 1500 g, corresponding to ≤ 32 weeks gestation, was numerically, but not statistically lower in the 17OHP-C arm (8.6%) vs. 13.9% in the vehicle arm. The prolongation of pregnancy, defined as the time from randomization to delivery or date last pregnant, was numerically longer, by a mean of 6 days, in the 17OHP-C group compared to the vehicle group. The mean gestational age at delivery was one week greater in the 17OHP-C group compared to the vehicle group (36.2 vs. 35.2 weeks, p=.031).

Neonatal mortality was numerically lower in the 17OHP-C group, but the between-group difference was not statistically significant (2.6% vs. 5.9%). The composite index of neonatal morbidity was lower in the 17OHP-C group (11.9%, 35/295 infants) than in the vehicle group (17.2%, 26/151 infants) but the between-group difference was not statistically significant.

The strength of the efficacy data relies on statistical significant reductions of PTBs at <37, < 35 and < 32 weeks gestation. The surrogate endpoints of reductions of PTBs at < 35 and < 32 weeks were thought by the advisory committee to predict a reduction in neonatal mortality and morbidity. The results of studies in the literature (see section 8.6) provide further support for the effectiveness of 17OHP-C for prevention of PTB; however, the small size and variable entry criteria for these studies limit the strength of their findings. The major weakness of this Application is that it relies on a single multicenter study for evidence of effectiveness.

1.3.3 Safety

Study 17P-CT-002. There were no maternal deaths. Eleven subjects discontinued because of an adverse event. Seven subjects were in the 17OHP-C arm: three with urticaria, two with injection site pain or swelling, one with arthralgia, and one with weight gain. Four subjects were in the vehicle arm: two with pruritus, one with urticaria, and one with injection site pain. The most common serious adverse events (SAEs) were congenital anomalies. The number and type of these anomalies appeared evenly distributed over the two treatment arms. There were three reports of a SAE in the mothers, all in the 17OHP-C arm; none were thought by the investigators

to be related to the study drug. The SAEs were: one subject with a pulmonary embolus 8 days after delivery; a case of cellulitis at the study medication site; and one case that included postpartum hemorrhage, respiratory distress and endometritis.

The most common adverse events (and the percentage of subjects reporting them in the 17OHP-C group) were injection site pain (34.8%), injection site swelling (17.1%), urticaria (12.3%), pruritus (7.7%), injection site pruritus (5.8%), nausea (5.8%), and contusion (5.5%). The most common adverse events (and the percentage of subjects reporting them in the vehicle group) were injection site pain (32.7%), urticaria (11.1%), contusion (9.2%), injection site swelling (7.8%), pruritus (5.9%), and neonatal death (5.9%).

Table B lists the numbers of miscarriages, stillbirths and neonatal deaths in each group. The observed reduction in neonatal deaths was offset by an increase in second trimester miscarriages and stillbirths. Thus, when considering overall mortality, there was no net survival benefit.

Table B. Miscarriages, Stillbirths, and Neonatal Deaths (Study 17P-CT-002)

Pregnancy Outcome	17OHP-C N=306 n (%)	Vehicle N=153 n (%)	Nominal P-value
Miscarriages <20 weeks gestation	5 (1.6)	0	0.17
Stillbirth	6 (2.0)	2 (1.3)	0.72
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.12
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.69**

This reviewer identified three out of nine complications of pregnancy reported by the Applicant in both the principal study 17P-CT-002 and the initial formulation study 17P-IF-001 where the percentage of affected subjects was numerically greater in the 17OHP-C arm. The pregnancy complications were gestational diabetes, oligohydramnios, and preeclampsia (see Table C)

Table C Selected Pregnancy Complications: Studies 17P-CT-002 and 17P-IF-001

Pregnancy Complication	Study	17OHP-C N (%)	Vehicle N (%)
Gestational Diabetes	CT- 002	17 (5.6)	7 (4.6)
	IF- 001	8 (8.6)	0 (0.0)
Oligohydramnios	CT- 002	11 (3.6)	2 (1.3)
	IF- 001	2 (2.2)	1 (1.9)
Preeclampsia	CT- 002	27 (8.8)	7 (4.6)
	IF- 001	6 (6.5)	2 (3.8)

Brief Summary of Safety Findings from Study 17P-IF-001. There was no increase in the incidence of miscarriage or stillbirth rate in the 17OHP-C treated subjects. There was only one case of miscarriage in each treatment arm. In terms of stillbirths, there were two cases in the vehicle arm compared to one case in the 17OHP-C arm. There were two neonatal deaths in the 17OHP-C arm, and none in the vehicle arm. The percentages of subjects with gestational diabetes and preeclampsia were higher in the 17OHP-C treated subjects (see Table C).

Study 17P-FU. There was no difference between the 17OHP-C and vehicle groups in the percentage of children who scored below the cutoff for at least one developmental area of the primary endpoint of the ASQ. The percentages of children who scored below the ASQ cutoff in each of the individual 5 developmental areas were similar in the 17OHP-C and vehicle groups. Developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age mates in physical, mental, social/emotional, or speech development, was reported for a comparable percentage in the 17OHP-C and vehicle groups.

Overall Safety Summary

There are no definitive safety issues that have been identified. There is a suggestion of an increase in miscarriages or stillbirths in 17OHP-C treated subjects. Injection site pain, swelling and pruritus were the most common AEs and reasons for discontinuation. There were no signals of developmental delay in the limited follow-up study of children.

1.3.4 Dosing Regimen and Administration

The dosing regimen was a weekly intramuscular injection of 250 mg of 17OHP-C beginning at 16^0 weeks to 20^6 weeks gestation and continued through 36^6 weeks gestation or birth. This dosing regimen appears to have been based on previously reported studies, most notably that of Johnson et al[26]. This dosing regimen has been used for off-label indications for several decades. Dose ranging studies were not submitted as part of this NDA.

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies were submitted as part of the NDA. Only a small number of subjects received concomitant medications that were likely to either increase or decrease the metabolism of 17OHP-C. Consequently, no conclusions about drug interactions can be made.

1.3.6 Special Populations

Women and children. All subjects in the principal study were pregnant women. 17OHP-C is to be used only in this population (i.e. pregnant women, including adolescents).

Renal and hepatic impairment. Subjects with renal or hepatic compromise were excluded form the clinical trials. Because the use of 17OHP-C may not be appropriate to prevent preterm birth in this population, no studies in pregnant women with significant renal or hepatic impairment are warranted.

Racial and age differences in efficacy and safety. Among the racial/ethnically diverse reproductive age female population studied, no significant differences in safety or efficacy were observed with the exception of a lower percentage of injection site reactions in Black subjects. The subjects in Study 17P-CT-002 were approximately 60% Black/African American, 26% White/Caucasian, 14% Hispanic, and 1% Other.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Adeza Biomedical has submitted New Drug Application (NDA) 21-945 for 17α-hydroxyprogesterone caproate (17OHP-C) injection for the proposed indication:

> "Prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth"

Preterm birth (PTB) is defined as a birth prior to 37 weeks 0 days (37^0) gestational age.

The proposed dosing regimen is a weekly intramuscular injection of 250 mg of 17OHP-C in 1 mL castor oil with 46% benzyl benzoate and 2% benzyl alcohol, beginning at 16 weeks 0 days (16^0) to 20 weeks 6 days (20^6) weeks gestation and used through 36^6 weeks gestation or birth.

2.2 Currently Available Treatment for Indication

Currently there is no drug product approved in the United States for prevention of preterm birth; however, 17OHP-C is being compounded by pharmacists and is being used widely for prevention of preterm birth in women at high risk. The medical need for an approved drug product for prevention of preterm birth is particularly acute because there also are no approved drug products currently marketed in the United States for the treatment of preterm labor. Although several drug products with tocolytic properties (i.e., stopping uterine contractions) are used off-label for treatment of preterm labor, randomized controlled trials have failed to demonstrate that these drugs improve perinatal outcomes.

2.3 Availability of Proposed Active Ingredient in the United States

17α-hydroxyprogesterone caproate is being compounded by pharmacists and is being used widely for prevention of preterm birth in women at high risk. Two mail surveys were sent to all board certified Maternal-Fetal Medicine (MFM) sub-specialists in the United States: one in December 2003 (response rate 42%) six months after the data submitted to this NDA was published in the New England Journal of Medicine in June, 2003, and the other in March 2005 (response rate 47%). In 2005, 67% of the respondents used progesterone to prevent spontaneous preterm birth compared to 38% in 2003. Other progestogens were used in addition to 17OHP-C; these physicians also used progestogens in women with other risk factors in addition to a previous spontaneous preterm birth.

2.4 Important Issues With Pharmacologically Related Products

17α-hydroxyprogesterone caproate was approved by the Food and Drug Administration (FDA) in 1956 for use in pregnant women (NDA 10-347; Delalutin®). The approved indications included the treatment of habitual and recurrent abortion, threatened abortion, and post-partum

"after pains." This approval was based largely on safety considerations in that it occurred prior to the FDA Drug Amendment of 1962, which required that drugs must have substantial evidence of efficacy in addition to evidence of safety in adequate and well-controlled trials. In 2000, the FDA withdrew approval for Delalutin. This action was taken at the request of the holder of the NDA because the holder was no longer marketing the drug. The action was not taken because of safety concerns. See Section 7.2.7 for an in-depth discussion of safety.

Published clinical studies with 17OHP-C have primarily supported the effectiveness of 17OHP-C for the prevention of preterm birth; however, these studies differed in design, enrollment criteria, endpoints, and length of treatment. This prompted the National Institute of Child Health and Development, via the Maternal-Fetal Medicine Units (MFMU) Network, to conduct a multicenter placebo-controlled trial to assess the efficacy of 17OHP-C for the prevention of PTB. On June 12, 2003, data from the MFMU Network clinical trial was published in the New England Journal of Medicine, reporting a benefit of 17OHP-C by reducing preterm birth at < 37 weeks.[27] Data from the MFMU Network clinical trial (referred to as Study 17P-CT-002 in this application) provide the primary support for the safety and efficacy of 17OHP-C for the prevention of preterm birth in this application.

2.5 Pre-submission Regulatory Activity

After data from Study 17P-CT-002 were published in the New England Journal of Medicine (Meis et al., 2003),[27] Adeza met with the Division of Reproductive and Urologic Products (hereafter referred to as DRUP or the Division) to discuss the possibility of using this data as the basis for an NDA for the indication of 17OHP-C for prevention of preterm birth. This clinical trial, however, was not originally intended for drug approval purposes.

The Division conveyed several recommendations and concerns to the Applicant during this and subsequent meetings. These included the following:

- A major concern was the lack of follow-up data, beyond the period of initial hospital assessment, of babies in which the mother had received 17OHP-C for the prevention of preterm birth. The Division requested that the Applicant obtain follow-up data on children through at least 2 years of age.
- A second major concern related to the drug product(s) used during the trial. The Sponsor was informed that complete chemistry, manufacturing and control (CMC) information would need to be provided about the drug product, including its purity and potency. The Applicant would need to provide information that the drug product used in the NIH sponsored clinical trial and the to-be-marketed formulation would be identical.

- The Division had some concerns about endpoints of Study 17P-CT-002 and the adequacy of these endpoints to support approval of a new drug product for marketing in the U.S, particularly since the NDA supporting the safety and effectiveness of 17OHP-C would be based primarily on the outcome of a single clinical trial. These concerns included:
  - The lack of any suggestion of improvement in overall mortality, and only a suggestions of an improvement in overall morbidity in the 17OHP-C treated subjects compared to the placebo treated subjects.
  - Clinical Trial 17P-CT-002 did not show a statistically robust effect for reducing the number of births at gestational ages <35 and <32 weeks, when infant morbidity/mortality is a much greater clinical problem in the U.S. The Division, however, recognized that the trial was not powered for these endpoints.
  - The primary endpoint of Clinical Trial 17P-CT-002 was a surrogate for pregnancy outcome (neonatal/infant morbidity and mortality). The Division indicated that its review would also consider what it believed to be the most important outcomes (overall survival of fetuses/infants and a significant reduction in serious morbidities from the time of enrollment rather than only an increase in gestational age, without other accompanying clinical benefits).
  - Normally, either two adequate and well-controlled studies or a single study with a robust and compelling outcome and strong supporting data would be required to support approval of a new drug product. There was a possibility that the data from Trial 17P-CT-002 would not be sufficient to demonstrate that 17OHP-C is safe and effective for the prevention of preterm birth.

2.6 Other Relevant Background Information

Significance of Preterm Birth

Preterm birth (PTB), birth prior to 37 weeks of gestational age, is the leading cause of neonatal mortality (infant death <28 days of life) and is a major cause of early childhood mortality and morbidity in the United States.[1] As many as half of all pediatric neurodevelopmental problems can be attributed to preterm birth.[2] The U.S preterm birth rate increased by 29% over the previous two decades to a high of 12.1% in 2002.[3] Most of this increase occurred in preterm births of 32-36 weeks gestational age and is thought to be due to the increasing frequency of pregnancy in women older than 35 years and the use of infertility treatments.[4] The rate for very early preterm births (< 32 completed weeks gestation) has remained stable at about 2% of all births; however, most perinatal/neonatal and infant mortality, and the most significant morbidity occurs in these infants.[3] Preterm births most often result from spontaneous preterm labor and preterm premature rupture of membranes (pPROM).[5,6,7] However, 20-30% of preterm births are considered "indicated" to avoid or minimize maternal/fetal complications.[8]

Rates of PTB in the United States differ profoundly among ethnic groups; the rate of PTB in non-Hispanic black births is twice as high as that of non-Hispanic white births. These disparities

remain even after adjusting for confounders such as education and occupation, suggesting a combination of genetic, environmental, and social factors as the etiology.[9,10,11,12,13,14] Accurate prediction and prevention of PTB remain elusive.[2,6-8,15-19] Most biomarkers to assess the risk of PTB have poor positive predictive value to guide clinical decisions.[2,8,15-20] Examples of risk factors include history of previous preterm birth; multifetal gestation; and cervical, uterine, and placental structural or physiologic abnormalities.

Prophylactic methods for prevention of preterm birth, including drugs, bed rest, or other interventions, have been shown in general to lack effectiveness. Tocolytic drugs may be given to reduce the frequency of uterine contractions. However, they have not been efficacious in preventing preterm birth nor have they resulted in improved newborn outcomes. Preterm birth has been described as a "common, complex disorder, stemming from heterogeneous composites of multiple gene-environment interactions."[21] Evidence supporting this includes findings of familial aggregation, non-Mendelian heritability, high rates of recurrence, and the existence of ethnic/racial disparities.

Pathophysiology of Preterm Birth

The "syndrome" of PTB is now understood as the clinical endpoint for a number of potential causes. Four major pathophysiologic pathways have been hypothesized:

(1) inflammation/infection with its associated maternal and fetal cytokine response
(2) maternal/fetal stress with generation of placental and fetal membrane-derived corticotropin-releasing hormone, which enhances placental estrogen and fetal adrenal cortisol production
(3) abruption or decidual hemorrhage with thrombin-induced protease expression and disturbances in uterine tone
(4) mechanical stretch due to multifetal pregnancy or polyhydramnios-induced abnormal uterine and cervical distension

Infection/inflammation is the only pathologic process for which a firm causal link with prematurity has been established and for which a defined molecular pathophysiology is known.[22] It has been estimated that 40% of all preterm births occur in mothers with intrauterine infection, which is usually subclinical. The lower the gestational age at delivery, the greater the frequency of intrauterine infection.[23] The most common pathway is via ascending organisms from the lower genital tract, more commonly from an alteration in the normal vaginal flora.[24] The organisms enter the amniotic cavity and then, in some cases, will gain access to the fetus which may result in fetal sepsis or the Fetal Inflammatory Response Syndrome (FIRS)[25], leading to possible death. The clinician managing preterm labor must balance the risk of subclinical infection, against the sequelae of prematurity, both having the potential for causing death.

Literature of 17OHP-C for Preventing PTB

The published literature includes several studies evaluating the efficacy of 17OHP-C in preventing preterm birth (see Table 1). Not included in this table is the publication by Meis PJ,

Klebanoff M, et al. that was based on the findings from Study 17P-CT-002 and is the focus of this Application.

Medical Reviewer's Comments

- *These studies varied in enrollment criteria, study design, length/dose of treatment and endpoints. However, all studies that enrolled subjects with a history of at least one previous PTB showed a numeric reduction in PTD in the 17OHP-C arm. In addition, the LeVine study (enrolled subjects with three previous SABs) and the Papiernik study (enrolled subjects with a "high risk" score) showed a reduction in PTB in the 17OHP-C arm. The only study that showed no treatment effect was the Hauth study, which enrolled women who were active duty military. There is no evidence that these women at increased risk for PTB.*

Table 1 Published Studies of the Efficacy and Safety of 17OHP-C in Preventing Preterm Birth

Investigator	Drug:Dose	Entry Criteria	Design	Number of Subjects	Start Tx	Stop Tx	Outcome % PTB[A]	No. of SAB[B]
LeVine 1964[1]	17P[D]: 500 mg weekly vs. Placebo	3 SABs	RCT, DB[C] Placebo 1:1	17P: 15 Placebo: 15	< 16 wks	36 wks	17P: 7/15 (46%) Placebo: 10/15 (66%)	17P: 3/15 Placebo: 7/15
Papiernik-Berkhauer 1970[2]	17P: 250 mg q 3 days vs. Placebo	High preterm risk score	RCT Placebo 1:1	17P: 50 Placebo: 49	28 – 30 wks	8 doses	17P: 4.1%) Placebo: (18.8%)	No data
Johnson et al 1975[3]	17P: 250 mg weekly vs. Placebo	2 SABs or 1PTB + 1 SAB or hx 2 PTBs	RCT, DB Placebo 1:1	17P: 18 (4 cerclage) Placebo: 22 (3 cerclage)	Booking < 24 wks	37 wks	17P: 0/18 (0%) Placebo: 9/22 (41%)	17P: 3/23 Placebo: 0/27
Hauth 1983[6]	17P: 1000 mg weekly vs. Placebo	Active duty military	RCT, DB	17P: 80 Placebo: 88	16 – 20 wks	36 wks	17P: (6.3%) Placebo: (5.7%)	No Data
Yemini 1985[4]	17P: 250 mg weekly + cerclage vs. Placebo	Hx of 2 SABs or 2 PTBs	RCT, DB Placebo 1:1	17P: 39 (39 cerclage) Placebo: 40 (40 cerclage)	Booking (12.2 wks av.)	37 wks	17P: 5/31 16.1%) Placebo: 14/37(37.8%)	17P: 8/39 Placebo: 3/40
Suvonnakote 1986[5]	17P: 250 mg weekly vs. no treatment	Hx of 1 PTB or 2 late SABs	Non-randomized	17P: 36 No Rx: 39	16 – 20 wks	37 wks	17P: 5/35 (14%) No Rx: 19/39 (49%)	No Data

[A] PTB=Preterm Births

[B] SABs=Spontaneous Abortions; Data for this outcome obtained both from the original articles and a meta-analysis by Keirse (see citation No. 2 below).

[C] RCT, Randomized Controlled Trial, DB=Double Blind

[D] 7P = 17OHP-C

1 LeVine L. Habitual abortion. A controlled clinical study of progestational therapy. West J Surg Obstet Gynecol. 1964;72:30-6.

2 Papiernik-Berkhauer E. Double blind study of an agent to prevent pre-term delivery among women at increased risk. Ref from Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Brit J Obstet Gynaecol. 1990;97(2):149-5

3 Johnson JW, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17 α-hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med. 1975;293(14): 675-80.

4 Yemini M, Borenstein R, Dreazen E, Apelman Z, Mogilner BM, .Kessler I, et al. Prevention of premature labor by 17 α-hydroxyprogesterone caproate. Am J Obstet Gynecol. 1985;151(5):574-7.

5 Suvonnakote T. Prevention of pre-term labour with progesterone. J Med Assoc Thai.1986; 69(10):538-42.

6 Hauth JC, Oilstrap LC 3rd, Brekken AL, Hauth JM. The effect of 17 α-hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. Am J Obstet Gynecol. 1983;146(2):187-90.

Source: Prepared by Medical Reviewer.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The conclusion of the chemistry review is that "this new drug application (21-945) is APPROVABLE from the perspective of chemistry, manufacturing, and controls. Issues regarding drug product photosensitivity and particulate matter, which impact the storage and expiration date for the drug product, remain unresolved".

The chemistry reviewer stated that the Applicant has not shown that the drug product is photostable. The recommendation is to submit a description of alternative packaging and to revise the drug product labeling to state that the vials should be protected from light. In addition, the proposed expiration date of 24 months for the drug product is not acceptable based on the submitted data; (b) (4) would be more appropriate.

The Office of Compliance has given an overall acceptable recommendation for the manufacturing and testing facilities.

The microbiology reviewer recommended approval from the standpoint of product quality microbiology. The reviewer was able to locate and review all of the necessary manufacturing process information related to microbiological drug product quality in the application. A meeting was held with the Applicant to discuss two information requests and the requested information was provided.

3.2 Animal Pharmacology/Toxicology

The pharmacology/toxicology team identified the following unresolved issues:

- "Based on the information available in the published literature, it appears that high doses of 17-HPC are associated with increased embryo lethality in several species. The nonclinical data provided is insufficient to calculate a no adverse effect level (NOAEL) in animals.
- There is insufficient nonclinical information on potential adverse effects on postnatal development including learning, behavior, and reproduction".

Based on the issues described above, this team made the following recommendations:

A. Recommendation on approvability: Approvable

B. Recommendation for nonclinical studies: A state of the art, GLP-compliant, multigenerational reproductive toxicology study which covers the stages of pregnancy covered in the clinic, is recommended to evaluate the safety of 17OHP-C on maternal and fetal health.

C. Recommendations on labeling: Although no teratogenicity was seen in mice or monkeys (Rhesus & Cynomolgus), it should be stated that fetal deaths were seen in the Rhesus reproductive toxicity study. No well-controlled nonclinical toxicity

studies have been conducted with 17OHP-C to support the indication of preterm labor"

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

In support of their application for the use of 17OHP-C for the prevention of preterm birth the Applicant submitted data from two active treatment clinical trials (study 17P-CT-002; study 17P-IF-001) and a follow-up safety study (study 17P-FU). An overview of these studies is presented in Table 2, Section 4.2.

Initial Formulation Study (Study 17P-IF-001)
This study began in February 1998, but treatment was terminated in March 1999 because the active study drug (17OHP-C) was recalled by its manufacturer, under the direction of the FDA, due to violations of manufacturing practices potentially affecting the potency of the drug. At the time of termination, only 150 of the proposed 500 subjects had been randomized and had started treatment, and no data analysis had been done. One hundred four (104) subjects (65 randomized to 17OHP-C and 39 randomized to vehicle) had ended their treatment prior to the study termination either because they had completed treatment with study drugs through week 36^6 or delivery or had terminated treatment prematurely for reasons other than recall of study drugs. The active study drug used in this terminated study is referred to as the Initial Formulation (IF). The data collected from subjects enrolled in the terminated study were analyzed separately in the NDA, and the results are also summarized separately.

Principal Clinical Trial (Study 17P-CT-002)
This study, which began in October 1999, randomized and treated 463 subjects who had at least one documented prior spontaneous preterm birth of a singleton, non-anomalous fetus. Of these, 418 subjects (90.3%) completed dosing through 36^6 weeks or birth: 279 (90.0%) in the 17OHP-C group and 139 (90.8%) in the vehicle group. This study was terminated prior to enrolling the proposed 500 subjects because the prespecified stopping criterion for efficacy was attained at an interim analysis.

Follow-up of Children from the 17P-CT-002 trial (Study 17P-FU)
This was a follow-up to Study 17P-CT-002. The follow-up study collected data with a validated child development instrument, the Ages and Stages Questionnaire (ASQ), a Survey Questionnaire concerning the health and development of the child, and a physical examination. The children were at least 2 years of age at the time of the follow-up assessments. The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received weekly intramuscular injections of 17OHP-C compared with weekly injections of vehicle during the pregnancy in Study 17P-CT-002. Only 14 of the original 19 sites were remaining in the Maternal Fetal Medicine Network at the time that the follow up study was conducted. Therefore,

approximately 80% of the children were eligible to participate. Of these eligible children, 278 enrolled: 194 from the 17OHP arm, and 84 from the vehicle arm.

4.2 Tables of Clinical Studies

Table 2 Clinical Studies of 17OHP-C in NDA 21-945

Protocol # /Status	Study Design	Study Population	Treatment Dose	Duration of Drug Treatment	Number of Subjects Enrolled	Number of Black/Non-Black Subjects	Mean Age (Range)
17P-IF-001 Terminated Mar 1999[A]	Double-blind, Placebo-controlled, Randomized 2:1 active treatment to Placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 37^0 wks gestation or delivery	Total: 150 17P: 94 Placebo: 56	Total: 95/55 17P: 54/40 Placebo: 41/15	26.2 yr (17, 42)
17P-CT-002 Completed Aug 2002[B]	Double-blind, Placebo-controlled, Randomized 2:1 active treatment to Placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 37^0 wks gestation or delivery	Total: 463 17P: 310 Placebo: 153	Total: 273/190 17P: 183/127 Placebo: 90/63	26.2 yr (16, 43)
17P-FU Completed Nov 2005	Observational long-term safety follow-up for Study 17P-CT-002	Infants discharged live in Study 17P-CT-002	None	No study treatment was administered	Total: 278 17P: 194 Placebo: 84	Total: 152/126 17P: 105/89 Placebo: 47/37	47.4 mo (30, 64)

[A] Study 17P-IF-001 was terminated early by the Sponsor when the manufacturer recalled the study drug. The last subject visit was in August 1999. Of the 150 subjects, 104 subjects (65 randomized to 17OHP-C and 39 randomized to vehicle) had ended their treatment prior to the study termination either because they had completed treatment with study drugs completed study treatment to 36^6 weeks of gestation or delivery or had withdrawn prematurely for reasons other than recall of study drugs.

[B] An independent Data and Safety Monitoring Committee (DSMC) reviewed the study data after 400 subjects had completed the study. Based on that interim dataset, the primary endpoint, birth $<37^0$ weeks of gestation, was significantly reduced and the p-value was below the p-value specified in predefined stopping rules. The DSMC recommended that enrollment in the study be stopped, so that no new subjects would be assigned placebo. By the time the study was stopped, 463 subjects had been enrolled, which was 92.5% of the proposed sample size of 500 subjects.

Source: Prepared by Medical Reviewer from final Study Reports.

4.3 Review Strategy

Data from three clinical trials were submitted and were reviewed by this medical officer. Study 17P-IF-001 was reviewed primarily for safety. Study 17P-CT-002, the principal study, was reviewed for both efficacy and safety. The findings from these two studies were not integrated,

since the potency and quality of the recalled drug in Study 17P-IF-001 was in question. Study 17P-FU-report was reviewed concerning the long term safety of the children who were born in the principal study. The report of this later study was also reviewed by a non FDA consultant, (b) (4)

4.4 Data Quality and Integrity

Three study sites were inspected by the Division of Scientific Investigation (DSI):

- Site # 8: John C. Hauth, M.D., investigator (Univ. of Alabama): 126 subjects enrolled; 86 treated with 17OHP-C.
- Site # 4: Baha Sibai, M.D., investigator (Univ. of Tennessee): 45 subjects enrolled; 30 treated with 17POH-C; (Dr. Sibai has moved to Cincinnati and Dr. Robert Elder is now the investigator at that site).
- Site # 20: Michael Varner, M.D., investigator (Univ. of Utah) : 43 subjects enrolled ; 29 were treated with 17OHP-C.

These sites were selected because these were the sites with the largest enrollment.
Inspection of only one site was completed during this review cycle: Dr. John Hauth of the University of Alabama Center for Women's Reproductive Health, Birmingham, Alabama. This clinical site was the largest enroller and the site had not been previously inspected.

The review by DSI stated: "At Dr. Hauth's site, 126 subjects were enrolled and the records for 42 subjects were reviewed for the primary efficacy endpoint (delivery date/gestation), inclusion/exclusion criteria, reporting of adverse events, informed consent, and drug accountability. No significant deviations were observed. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication."

Inspections/reports of the other two sites will be completed during the next review cycle.

4.5 Compliance with Good Clinical Practices

According to the Applicant "This study was conducted in a manner consistent with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki, and Parts 50, 54, 56, and 312 of Title 21 of the Code of Federal Regulations."
The protocol and the informed consent form (ICF) were reviewed and approved by an Institution Review Board (IRB) at each participating site prior to initiation of the study. Written informed consent was obtained from each patient before entry into the clinical trial. Women who were not fluent in English were enrolled by a person who was fluent in their language, and verbal and written informed consent were obtained in their language; if a person fluent in their language was not available, the women were not included. According to the Applicant, "certification of each study center (as described in the Manual of Procedures in Section 16.1.11) was required and a training session for the nurse coordinator at each site was held at the (b) (4) (b) (4) before recruitment of patients.

Medical Reviewer Comment

- *Based on information provided by the Applicant and available information form DSI, it appears that the principal clinical trial was conducted in accordance with Good Clinical Practice.*

4.6 Financial Disclosures

On April 12, 2006 a signed certification of Financial Interests and Arrangements of Clinical Investigators was provided by Durlin E. Hickok, M.D., Vice President of Medical Affairs for Adeza Biomedical. He attested that based on information obtained from the sponsor of the clinical trials (i.e., the NIH) or from participating clinical investigators, the listed clinical investigators (all investigators in studies 17P-IF-001, 17P-CT-002, and 17P-FU) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in CFR 54.2(b)); and were not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

17 α-hydroxyprogesterone caproate (17OHP-C) is not fractionated to a significant degree into the free sterol and the fatty acid residue following IM injection in humans. The active ingredient 17OHP-C is therefore fully bioavailable. 17OHP-C is 95% bound to plasma proteins *in vitro* (human plasma). The drug is excreted exclusively in the form of conjugates, approximately 80% via the liver and approximately 20% via the kidneys. The elimination half-life is approximately 6 days. The depot injection of drug is depleted after 3-4 weeks.

The applicant submitted very limited pharmacokinetic and clinical pharmacology information in non-pregnant and pregnant women. Two studies were reviewed by Doanh Tran, PhD. clinical pharmacology reviewer of this NDA and his review is summarized below:

- Limited pharmacokinetics (PK) information in pregnant women is derived from a published report (Davis 1960) where single doses of Carbon-14 labeled 17OHP-C were given to four pregnant women at 10 to 12 weeks gestation. The data showed that approximately 50% of radioactivity was excreted in the feces and an average of 29.7% of radioactivity was excreted in urine over 12 - 15 days. Maximum total plasma radioactivity was reached 5 days following IM injection followed by a slow decline. The dose in mg and formulation were not specified.
- PK information in non-pregnant women is derived from a literature report by Onsrud et al. (1985) using a formulation that is very similar to the to-be-marketed formulation. In this

report, single dose of 1000 mg 17-OHP-C in endometrial cancer patients (n=5) resulted in a mean serum C_{max} of 27.8ng/ML (65 nM), T_{max} of 4.6 days, and terminal half-life of 7.8 days.

Medical Reviewer's Comments

- *It would be useful to obtain additional drug metabolism and drug interaction information to provide clearer direction to optimize therapy.*
- *In consultation with the clinical pharmacologist (Dr. Tran), the following studies are recommended as part of a postmarketing commitment (see clinical pharmacology review):*
    1. *Characterize the pharmacokinetics of 17OHP-C and its metabolites in pregnant women (includes both plasma and urine concentrations) at several periods throughout the pregnancy. The periods should be spaced out evenly to allow assessment of PK changes as a pregnancy progresses. For example, a 3-period study design may include assessments at 16 – 20, 24 – 28, and 32 – 34 weeks gestation.*
    2. *Assess the 17OHP-C exposure response relationship via sparse sampling of all subjects.*
    3. *Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on 17OHP-C PK.*
    4. *Assess the effect of body weight on the pharmacokinetics of 17OHP-C using samplings specified in comment 2.*
    5. *Examine the effect of hepatic impairment on 17OHP-C pharmacokinetics.*

5.2 Pharmacodynamics

The Applicant was asked to provide the percentage of subjects who delivered at less than 37 weeks by selected BMI categories.

The mean, median, and range of BMI for each treatment arm are shown in Table 3.

Table 3 BMIs (kg/m^2) for Subjects in Study 17P-CT-002

	17OHP-C	Vehicle	Total subjects
N	298	149	447
Median	25.1	24.1	24.6
Mean	26.9	26.0	26.6
S.D.	7.9	7.0	7.6
Min, Max	15.2, 72.2	16.1, 50.7	15.2, 72.2

Source: Information request response submitted by Applicant on Sept 12, 2006

A breakdown of subjects delivering < 37 weeks gestation by BMI did not reveal any apparent differences in the percentage of PTB except for a small numerically higher number of PTBs in

subjects with a low BMI (less than 18 kg/m^2) as shown in Table 4. In the vehicle group, the highest proportion of PTBs also occurred in subjects with a BMI of <18 kg/m^2.

Table 4 Percent of Deliveries < 37 weeks gestation by BMI (kg/m^2) in ITT Population *

	17OHP-C		Vehicle		Total subjects	
# of subjects	310		153		463*	
BMI	n / N	(%)	n / N	(%)	n / N	(%)
< 18	10/23	**(43.5%)**	6/7	(85.7%)	16/30	(53.3%)
18 – 25	53/144	**(36.8%)**	54/86	(62.8%)	107/230	(46.5%)
26 – 30	19/54	**(35.2%)**	15/28	(53.6%)	34/82	(41.5%)
> 31	25/77	**(36.4%)**	7/28	(25.0%)	35/105	(33.3%)
Overall	110/298	**(36.9%)**	82/149	(55.0%)	192/447	(42.0%)

* Note ITT Population is all randomized subjects. Subjects with missing outcome data are classified as having preterm delivery < 37 weeks (treatment failure). BMI is missing for 16 of the 463 randomized subjects.
Source: Table 1, information request response submitted by Applicant on Sept 12, 2006

Medical Reviewer's Comments

- *The finding of no difference in percentage of deliveries less than 37 weeks gestation regardless of BMI (except for possibly in the subjects with the lowest BMI) suggests that 17OHP-C is equally effective in obese subjects compared to normal weight subjects.*
- *The finding of a relative increased preterm birth rate in subjects with low BMI (less than 18 kg/m^2) in both the 17OHP-C and vehicle treatment groups is consistent with findings in many other studies: women with a low BMI are at significantly increased risk of having a preterm birth.*

5.3 Exposure-Response Relationships

Exposure-response studies (dose selection) were not done; there were no phase 2 studies as part of this application and only a single dose (250 mg/week) was studied in the Phase 3 trials. See comments in section 5.1. Dose selection was based on previously reported studies in the literature in which 250 mg/week appeared to be efficacious in reducing the incidence of PTBs.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Applicant's proposed indication for 17α-hydroxyprogesterone caproate (17OHP-C) injection is:

> "Prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth"

6.1.1 Methods

The 17P-IF-001 and 17P-CT-002 studies were randomized, placebo-controlled, efficacy and safety studies of 17OHP-C in pregnant women, from 16^0 to 20^6 weeks gestation, who had a history of at least one spontaneous preterm birth, defined as delivery from 20^0 to 36^6 weeks gestation following spontaneous preterm labor (PTL) or preterm premature rupture of membranes (pPROM). Active study drug consisted of 17OHP-C (250 mg/mL) in castor oil with 46% benzyl benzoate and 2% benzyl alcohol. Inactive (vehicle) study drug contained all the excipients of the active drug, but did not contain 17OHP-C. Study drugs were administered once weekly by intramuscular injection.

The principal safety and efficacy study (17P-CT-002) was conducted at 19 investigational sites in the United States. All sites were university hospital centers and were members of the NICHD MFMU Network (see Table 5 in section 6.1.4 for a list of sites and number of subjects enrolled and treated at each of these sites). All patients who presented at the study centers for prenatal care before 20^3 weeks gestational age were eligible for screening.

6.1.2 General Discussion of Endpoints

Primary Objective and Primary Endpoint. The primary objective of the initial study (study 17P-IF-001) and the principal safety and efficacy study (study 17P-CT-002) was to determine if, compared with placebo, 17OHP-C treatment initiated before 21^0 weeks gestation reduces the risk of preterm birth (birth $<37^0$ weeks gestation) in women who have previously experienced a spontaneous preterm birth. All deliveries occurring from the time of randomization (which occurred immediately before the first injection of study drug) through 36^6 weeks gestation, including miscarriages (i.e., spontaneous abortions) and stillbirths, were counted in the primary outcome. Thus, the primary efficacy population was a true intent-to-treat population. The primary endpoint was the proportion of subjects in each treatment arm who delivered at < 37 weeks gestational age.

Secondary Objectives. The secondary objectives defined in the protocols included both maternal and neonatal outcomes. Maternal objectives were to determine the following in women with a previous spontaneous preterm birth:

- Whether treatment with 17OHP-C reduces the use of tocolytic therapy and/or cervical cerclage.
- Whether treatment with 17OHP-C reduces neonatal morbidity/mortality.

Neonatal outcomes considered secondary efficacy measures included: birthweight; score reflecting condition of neonate (Apgar score); admission to the neonatal intensive care unit (NICU); infant hospital days; number of days of neonatal respiratory therapy; stillbirths; neonatal deaths; neonates with respiratory distress syndrome (RDS); intraventricular hemorrhage (IVH); bronchopulmonary dysplasia (BPD); necrotizing enterocolitis (NEC); early onset of neonatal sepsis; seizures; retinopathy of prematurity; and transient tachypnea. In addition, the percentage of infants who received ventilator support, and the percentage of infants who received supplemental oxygen were provided.

Based on communications with the FDA, the following secondary endpoints were added to the analyses of Study 17P-CT-002:

- Whether treatment with 17OHP-C, compared to placebo, reduces the risk of preterm birth at <35 weeks gestation.
- Whether treatment with 17OHP-C, compared to placebo, reduces the risk of preterm birth at <32 weeks gestation.
- Whether treatment with 17OHP-C, compared to placebo, reduces overall neonatal morbidity/mortality based on a composite measure of neonatal morbidity and mortality.

6.1.3 Study Design

Both Studies 17P-IF-001 and 17P-CT-002 were multicenter, randomized, vehicle-controlled, double-masked clinical trial to determine if weekly intramuscular injections of 17OHP-C reduce the incidence of preterm birth in pregnant women who have a history of spontaneous preterm delivery.

All patients who presented at the study centers for prenatal care before 20^3 weeks gestational age were eligible for screening. Documentation of previous deliveries was reviewed to ensure the patient met the inclusion criteria. If an abdominal ultrasound examination had not been performed at 14 weeks gestation or later for the study pregnancy, one was arranged prior to randomization into the clinical trial to confirm gestational age and screen for congenital anomalies. Also prior to randomization, a single injection of the vehicle drug product was administered to potential subjects from 15^0 to 20^3 weeks gestation, to assess the subject's tolerance of the injection.

Qualifying subjects were randomized in a 2:1 ratio to 17OHP-C or placebo. The following information was obtained for randomized patients during a patient interview, followed by a review of the patient's chart:

1. Demographic information: age, race.
2. Medical history: pre-pregnancy weight, height, sexually transmitted disease history, history of douching.
3. Obstetrical history including outcome of all prior pregnancies.
4. Social history: marital status, years of education, alcohol use, tobacco use, and illicit drug use.
5. Project gestational age and estimated date of confinement.

At each study visit, in a non-directive fashion, the subject was asked if she had experienced any side-effects or symptoms since the last visit that **she** considered associated with the study medication or medication administration. She was also queried about the use of corticosteroids and antibiotics since her last visit. In addition, at each weekly visit, salivary specimens for estriol and progesterone levels were collected, frozen, and stored at the study center for later analyses; however, these specimens have not been analyzed. No attempt was made to alter or

mandate clinical management of subjects during the study. However, the use of prophylactic tocolytic drugs was discouraged.

Study drug was administered weekly by intramuscular injection through 36^6 weeks gestation or delivery, whichever occurred first. Routine prenatal care was continued at each site in the customary fashion.

Mothers and infants were followed until they were discharged from the hospital following delivery, at which time relevant data from labor, delivery, and nursery records were documented.

Inclusion Criteria. Subjects had to meet all of the following criteria at screening to be eligible for enrollment into the study:

1. Gestational age between 16^0 weeks and 20^6 weeks at the time of randomization, based on clinical information and evaluation of the first ultrasound.
2. Documented history of a previous singleton spontaneous preterm birth. Spontaneous preterm birth was defined as delivery from 20^0 to 36^6 weeks gestation following spontaneous preterm labor or preterm premature rupture of membranes. Where possible, the gestational age of the previous preterm birth (referred to as the qualifying birth) was determined. If the gestational age at delivery was obtained directly from the medical record and more than one gestational age appeared, the latest was used. The qualifying delivery could not be an antepartum stillbirth.

Exclusion Criteria. If any of the following criteria applied, the subject was not eligible to enroll into the study:

1. Multifetal gestation.
2. Known major fetal anomaly or fetal demise. An ultrasound examination after 14 weeks gestation had to be performed to rule out fetal anomalies.
3. Progestogen treatment during current pregnancy.
4. Heparin therapy during current pregnancy or history of thromboembolic disease.
5. Maternal medical/obstetrical complications including:
   a. Current or planned cerclage;
   b. Hypertension requiring medication;
   c. Seizure disorder.
6. Prenatal follow-up or delivery planned elsewhere (unless the study visits could be made as scheduled and complete outcome information obtained).
7. A 14^0 to 20^6 week ultrasound could not be arranged before randomization.
8. Participation in an antenatal study in which the clinical status or intervention could have influenced gestational age at delivery. Subjects enrolled in any of the following MFMU Network studies during this period were ineligible for the trial: "Randomized Clinical Trials of the Effect of Metronidazole on Pregnancy Outcome in Women Infected with T. Vaginalis or Bacterial Vaginosis," "Randomized Trial of Metronidazole Plus Erythromycin to Prevent

Preterm Birth in Women with Elevated Cervical/Vaginal Oncofetal Fibronectin," "Randomized Clinical Trial of Theophylline versus Inhaled Beclomethasone," and "The Effects of Asthma and Treatment Regimens on Perinatal Outcome."

9. Participation in this trial in a previous pregnancy. Subjects who were screened in a previous pregnancy, but not randomized, were not excluded.

The MFMU Network Data Safety Monitoring Committee (DSMC) periodically reviewed safety and efficacy data during the conduct of this study. On 03 October 2000, the DSMC reviewed the first interim report since the start of the study in October 1999. The report included data on 176 randomized patients and outcome data on 76 randomized patients. The DSMC recommended that the trial continue. On 21 February 2002, the DSMC reviewed results from the second interim analysis, which was based on 446 patients randomized before 16 January 2001 and outcome data on 351 patients. At that time the DSMC recommended that recruitment be discontinued because the boundary for the test of significance of the primary outcome, preterm delivery $<37^0$ weeks, had been crossed, indicating that 17OHP-C had shown benefit. They further recommended that subjects who were already randomized continue on study drug through 36^6 weeks gestation or delivery without having their treatment assignment disclosed

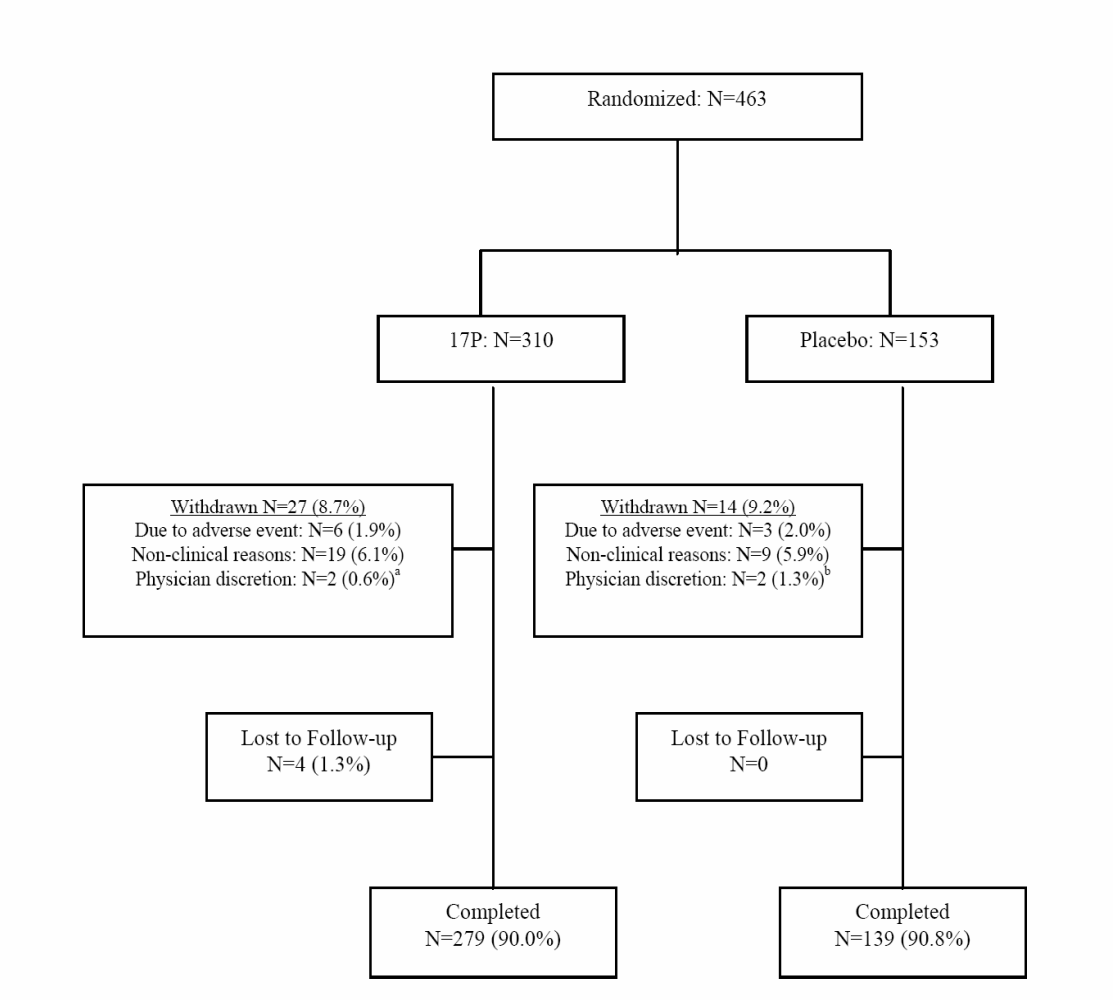
6.1.4 Efficacy Findings

Study 17P-CT-002 (Primary Efficacy and Safety Study)

Subject Disposition

A total of 463 subjects were randomized at 19 study centers in the U.S (Figure 1). Four hundred eighteen (418; 90.3%) subjects completed injections through 36^6 weeks gestation or delivery, whichever occurred first: 279 (90.0%) in the 17OHP-C group and 139 (90.8%) in the placebo group. Early discontinuation of treatment with study drug occurred at a similar rate in both treatment groups (8.7% 17OHP-C vs. 9.2% placebo). Most of these subjects discontinued due to "non-clinical reasons," which were not further defined by the Applicant (6.1% vs. 5.9%); those potentially due to adverse events (AEs) are discussed in Section 7.13. Four (<1.0%) subjects, all in the 17OHP-C group (<1.0%), were lost to follow-up.

Figure 1 Overview of Subject Disposition in Study 17P-CT-002



Note: "Withdrawn from the study" was defined as the patient no longer received study drug. "Lost to follow-up" was defined as the patient's delivery data could not be obtained. "Completed the study" was defined as the patient did not withdraw from the study and was not lost to follow-up.

[a] In the 17P (17OHP-C) group, Investigators stopped the treatment of one patient due to injection site reactions and another patient due to pPROM, which was not considered an AE. Therefore, 7 (2.2%) patients in the 17P group discontinued due to AEs.

[b] In the placebo (vehicle) group, Investigators stopped the treatment of one patient due to a potential allergic reaction and another patient due to pPROM, which was not considered an AE. Therefore, 4 (2.6%) patients in the placebo group discontinued due to AEs.

Source: Section 10.1, Figure 10-1, Final Report for Study 17-CT-002.

The number of subjects enrolled at each of the 19 study centers is listed in Table 5. Almost 30% of the subjects (126 of 463) were enrolled at a single center – University of Alabama.

Table 5 Enrollment of Subjects by Study Center, Sorted by Number Enrolled at the Center

Center #	Name	# Enrolled
8	University of Alabama	126
4	University of Tennessee	45
20	University of Utah	43
18	University of Texas Southwestern	39
2	University of Pittsburgh	36
15	Ohio State University	28
9	Wayne State University	24
21	Thomas Jefferson University	24
13	Wake Forest University	22
11	University of Cincinnati	13
19	University of Texas San Antonio	13
17	University of Miami	11
23	Columbia University	11
14	University of Chicago	7
25	Case Western University	6
22	Brown University	5
26	University of Texas Houston	4
27	University of North Carolina, Chapel Hill	4
28	Northwestern University	2

Source: Table 1, 17P-CT-002 Final Study Report.

Primary Endpoint (Applicant's Original Analyses)

The proportions of deliveries that occurred prior to 37 weeks gestation based on the ITT population and on all available data are summarized in Table 6. In the ITT population, 115 of 310 ((37.1%) in the 17OHP-C group had a delivery < 37 weeks gestation. In the placebo group, 84 of 153 subjects (54.9%) had a delivery < 37 weeks gestation. The difference was statistically significant.

Table 6 Percentages of Subjects with Delivery <37^0 Weeks Gestation (Applicant's Analysis)

Data Source	17OHP-C		Vehicle		Nominal P-value [A]	Treatment difference and 95% Confidence Interval [B]
	N	n (%)	N	n (%)		
ITT population	310	115 (37.1)	153	84 (54.9)	0.0003	-17.8% [-28%, -7%]
Only available data	306	111 (36.3)	153	84 (54.9)	0.0000	-18.6% [-29%, -8%]

ITT population was all randomized subjects. The 4 subjects with missing outcome data were classified as having a preterm birth of <37^0 weeks (i.e., treatment failure). "Only available data" does not include the 4 subjects with missing outcome data.

[A] Chi-square test. Adjusting for interim analyses, p-values should be compared to 0.035 rather than the usual 0.05.

[B] Confidence interval (CI) calculated by FDA, adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, a p-value boundary of 0.035 was used for the adjustment (equivalent to a 96.5% confidence interval).

Source: Modified from Table 11-3, Final Report for Study 17P-CT-002.

Medical Reviewer's Comments

- *The 95% confidence intervals for the difference between treatment groups in the percent of deliveries occurring at <37 weeks gestation suggest that the true proportion of preterm deliveries in the 17OHP-C group could range from -7 to -28% fewer than the proportion in the placebo group. This finding supports the Applicant's claim that treatment with 17OHP-C, compared to placebo, had a statistically significantly effect in reducing the proportion of deliveries <37 weeks.*
- *The preterm birth rate of 54.9% in the vehicle arm was considerably greater than the background rate of 36% used to power this study. The rate of 54.9% preterm births, is also considerably higher that of the control arm (36%) in another Maternal-Fetal-Medicine Network study, the Home Activity Uterine Monitoring study.*
- *The PTB rate of 37.1% in 17OHP arm is no lower than the PTB rate of 36% in the control arm of the Home Activity Uterine Monitoring study.*

Subjects who delivered prior to 37 weeks gestation also were classified (1) by the gestational age of the previous qualifying spontaneous preterm birth (SPTB) using the intervals of 20^0- < 28 weeks, 28^0- < 32 weeks, 32^0- < 35 weeks, and 35^0- < 37 weeks), (2) by race (Black [non-Hispanic Black] and Non-Black), and (3) by number of previous preterm births (1, 2, and ≥3) (see Table 7)

Table 7 Percentages of Subjects with Delivery <37 Weeks by Gestational Age of Qualifying Birth, Race, and Number of Previous Preterm Deliveries

Characteristic	17OHP-C n/N (%)	Vehicle n/N (%)
Previous SPTB (qualifying birth) by gestational age		
20^0 - <28 weeks	33/82 (40.2)	19/29 (65.5)
28^0 - <32 weeks	21/66 (31.8)	17/30 (56.7)
32^0 - <35 weeks	30/84 (35.7)	27/55 (49.1)
35^0 - <37 weeks	31/78 (39.7)	21/39 (53.8)
Race		
Black	66/183 (36.1)	47/90 (52.2)
Non-Black	49/127 (38.6)	37/63 (58.7)
Number of previous preterm births (PTBs)		
1 prior PTB	74/224 (33.0)	40/90 (44.4)
2 prior PTB	27/56 (48.2)	31/46 (67.4)
≥ 3 prior PTB	14/30 (46.7)	13/17 (76.5)

Data based on ITT Population (all randomized subjects). The 4 subjects with missing outcome data were classified as having a preterm birth <37^0 weeks (i.e., treatment failure).

SPTB = spontaneous preterm birth; PTB = preterm birth.

n = number of subjects in a specific category who delivered study pregnancy at <37^0 weeks gestation
N = total number of subjects overall in a specific category.

Source: Table 11-4, Final Report for Study 17-CT-002.

Rates of preterm birth at <37 weeks did not appear to differ significantly according to the gestational age of the qualifying delivery in either treatment group (with the possible exception of the category of 20^0 - <28 weeks in the placebo group). For all intervals of gestational age, the rates of preterm birth <37 weeks were numerically lower in the 17OHP-C treatment group.

The percentage of Black subjects in Study 17P-CT-002 was 59% in both groups. 17OHP-C, compared to vehicle, reduced the rate of preterm birth of <37 weeks gestation for both the Black (36.1% vs. 52.2%) and the Non-Black (38.6% vs. 58.7%) populations.

Subjects with more than one previous preterm birth, regardless of treatment group, had higher rates of preterm births for the study pregnancy than did subjects with only one previous preterm birth. The rates of preterm births in the 17OHP-C treatment group were numerically lower, compared to vehicle, for subjects with one previous preterm birth (33% vs. 44%), two previous preterm births (48% vs. 67%), and three or more previous preterm births (47% vs. 77%). If the last two categories were combined, the incidence of preterm birth in this study for subjects with more than one previous preterm birth was 48% in the 17OHP-C group compared with 70% in the placebo group.

Medical Reviewer's Comment

- *The reduction in preterm birth at <37 weeks gestation appears to be independent of race, number of qualifying preterm deliveries, or gestational age of qualifying preterm birth.*
- *The reduction in preterm birth at <37 weeks gestation appears greater in women with more than one previous PTB: 33% 17OHP-C vs. 44% vehicle in women with one previous PTB, compared to 48% 17OHP-C vs. 70% vehicle in women with more than one previous PTB. This suggests the greater the risk for PTB, the greater the efficacy of 17OHP-C.*
- *In the United States, the rate of preterm births in the general Black/African American population is almost twice that in the general Non-Black population; however, the rate was nearly identical in this study.*

Secondary and Additional Post Hoc Endpoints (Applicant's Analyses)

Proportion of Deliveries <35 and <32 Weeks Gestational Age (Applicant's Original and Revised Analyses)

Applicant's Original Analysis. At the request of DRUP, the Applicant also calculated the proportion of deliveries occurring at <35 weeks gestation and < 32 weeks gestation. DRUP made this request because of the increased morbidity associated with earlier premature deliveries. The proportion of deliveries < 35 weeks gestation (21.6% vs. 30.7%) and <32 weeks gestation (12.6% vs. 19.6%) were lower in the 17OHP-C group compared with the placebo group (see Table 8). This Table provides the Applicant's original analysis, which considers the 4 subjects with missing outcome data as treatment failures from the time of randomization.

Table 8 Percentages of Subjects with Delivery <35 and <32 Weeks Gestation (Applicant's Original Analysis)

Pregnancy Outcome	17OHP-C N=310 n (%)	Vehicle N=153 n (%)	Nominal P-value [A]
Delivery <35	67 (21.6)	47 (30.7)	0.0324
Delivery <32	39 (12.6)	30 (19.6)	0.0458

Data presented are from the ITT population (i.e., all randomized subjects). The 4 subjects with missing outcome data were classified as having a preterm birth at $<35^0$ and $<32^0$ weeks (i.e., treatment failures at all times).
[A] Adjusting for interim analyses, p-values should be compared to 0.035 rather than the usual 0.05.
Source: Table 11-5, Final Report for Study 17-CT-002.

Medical Reviewer's Comments

- *The p-values presented in Table 8 should be interpreted with caution for several reasons:*
  1. *there were two interim analyses and a final analysis and*
  2. *multiple endpoints, likely to be correlated with each other and with the primary endpoint, were analyzed.*

- *According to the FDA biostatistician, the p-values at all gestational ages should be adjusted for the two interim and final analyses.*

Applicant's Revised Analyses Based on discussions between the FDA biostatistician and the Applicant, the Applicant revised several of their analyses. The revisions were focused on using all available data for the ITT population. Specifically, all available data for subjects who were lost to follow-up were used in the revised analyses instead of considering these subjects as treatment failures at all analysis times.

Table 9 Percentages of Subjects with Delivery <35, <32, and <30 Weeks Gestation (Applicant's Revised Analysis)

Pregnancy Outcome	17OHP-C N=310 n (%)	Vehicle N=153 n (%)	Nominal P-value [A]
Delivery <35	66 (21.3)	47 (30.7)	0.0263
Delivery <32	37 (11.9)	30 (19.6)	0.0273
Delivery <30	30 (9.7)	24 (15.7)	0.0581

Data presented are from the ITT population (i.e., all randomized subjects). The 4 subjects with missing final outcome data (i.e. gestational age at delivery) were classified as having a preterm birth (i.e., treatment failures) immediately after the last visit at which they were determined to still be pregnant.
[A] Adjusting for interim analyses, p-values should be compared to 0.035 rather than the usual 0.05.
Source: Applicant's submission of August 23, 2006, Table I.

Medical Reviewer's Comment

- *This revision, which includes the lost to follow-up subjects for which interim outcomes were known, demonstrates a more favorable outcome for the 17OHP-C arm; however, the FDA dose not agree with the Applicant's contention that no adjustments for the interim analyses are required.*

FDA Analysis - Proportions of Deliveries at <37, <35 and <32 Weeks Gestational Age

The FDA's analysis of the effects of treatment with 17OHP-C, as compared to placebo, on the percentage of deliveries at <37, <35, <32, and <28 weeks gestation is shown in Table 10 At each cut point of weeks <37, <35, and <32, the percentage of deliveries was numerically lower in the 17OHP-C treatment arm. The point estimates of the differences between the percentage of births at each gestational age ranged from -17.8% (at <37 weeks) to -7.7% (at <32 weeks). The upper limits of the 95% confidence intervals (adjusted to preserve the overall Type I error rate of 0.05) of the differences between treatment groups approached, but did not cross zero at <35 weeks and <32 weeks gestation. There was no difference between treatment groups for the percentages of deliveries <28 weeks.

Table 10 Proportion (95% Confidence Interval) for Delivery at <37 Weeks, <35 Weeks, <32 Weeks, and <28 Weeks Gestational age (ITT Population, FDA Analysis)

Data Source	17OHP-C[a] (N=310)	Vehicle (N=153)	Treatment difference and 95% Confidence Interval, (adjusted for interim analyses)[b]
	%	%	
<37 weeks	37.1	54.9	-17.8% [-28%, -7%]
<35 weeks	21.3	30.7	-9.4% [-18.7%, -0.2%]
<32 weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]
<28 weeks	9.4	10.5	-1.1% [-7.4%, 5.2%]

[a] Four 17P-treated patients were losses-to-follow-up. They are counted as deliveries at their gestational ages at time of last contact (18.6, 22.0, 34.4 and 36.6 weeks, respectively).
[b] The confidence intervals have been adjusted for the 2 interim analyses and the final analysis. To preserve the overall Type I error rate of 0.05, the adjusted confidence intervals (equivalent to a 96.6% confidence interval) use the final p-value boundary of 0.0345.

Medical Reviewer's Comment

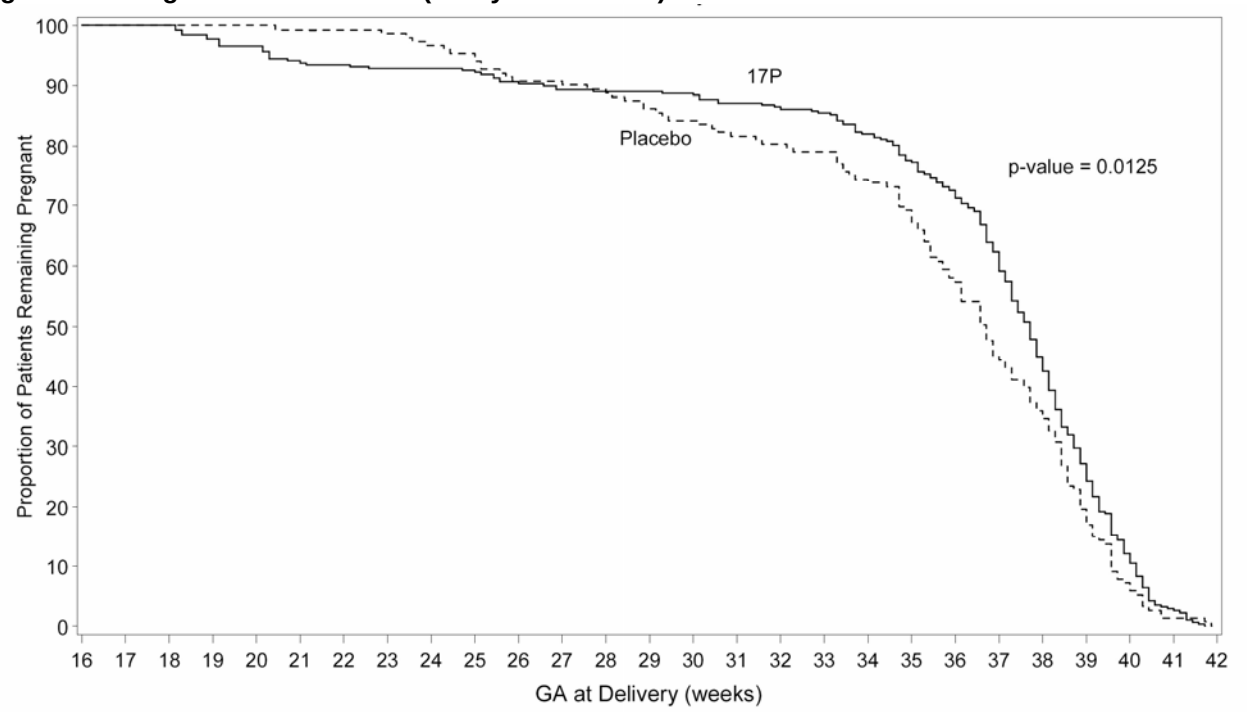
- *The upper limits of the 95% confidence intervals for the differences between treatment groups for deliveries at <35 weeks and <32 weeks gestation approached, but did not cross zero thereby meeting the generally accepted criteria for statistical significance. This analysis is more conservative than that of the Applicant in that it adjusts for the 2 interim and final analyses. In the Applicant's analysis (see Table 9) no adjustment for these interim analyses was made.*
- *This Reviewer recognizes that this clinical trial was not powered to demonstrate a difference in the rates of deliveries between the 2 treatment groups at either <35 weeks or <32 weeks gestation. However, because the Applicant is seeking approval for 17OHP-C based on (1) only a single clinical trial and (2) a surrogate endpoint of neonatal/infant morbidity and mortality, inability to demonstrate a robust effect at either <35 weeks or <32 weeks gestation is an important consideration in assessing the overall effectiveness of 17OHP-C for the proposed indication.*

Mean Gestational Age at Delivery and Duration of Pregnancies (Applicant's Analysis)

The mean gestational age at delivery for subjects with available outcome data (306 in the 17OHP-C group and 153 in the placebo group) was one week greater in the 17OHP-C group (36.2 weeks vs. 35.2 weeks). The gestational ages at delivery ranged from 18.1 to 41.6 weeks. The median prolongation of pregnancy (defined as the time from randomization until delivery or date that the subject was last confirmed to be pregnant) was higher in the 17OHP-C group compared to the placebo group (131 days vs. 125 days).

A Kaplan-Meier analysis of the proportion of subjects remaining pregnant as a function of gestational age is provided in Figure 2.

Figure 2 Time to delivery as a function of gestational age, using staggered entry based on the gestational age at randomization (Study 17P-CT-002)



Source: Applicant Response to FDA's request dated 7/20/06

The results of the log-rank test show that the difference in the shapes of the curves in Figure 2 is statistically significant (p-value = 0.0125). Prior to approximately 25 weeks gestation, a numerically greater proportion of subjects randomized to the 17OHP-C arm delivered at each gestational age; after 28 weeks gestation, a greater proportion of subjects randomized to the vehicle arm delivered at each gestational age.

Medical Reviewer's Comments

- *The increased proportion of delivered subjects in the 17OHP-C group, relative to the vehicle group, up to a gestational age of 25 weeks was due largely to the 5 miscarriages (spontaneous abortions) at <20 weeks gestation in the 17OHP-C group and other early fetal losses up to 25 weeks gestation. No miscarriages (spontaneous abortions) at <20 weeks gestation were reported in the vehicle group. Whether treatment with 17OHP-C contributed to these early pregnancy losses is not known.*
- *A second randomized clinical trial (or data from other sources) would be helpful in assessing whether treatment with 17OHP-C may be associated with an increase in early pregnancy loss..*

Consistency Across Centers (FDA Analysis)

The University of Alabama enrolled 126 out of 463 subjects, which accounts for about 25% of the total enrollment. To determine the impact of the University of Alabama on the results, the FDA statistician did a stratified analysis: one stratum contains the University of Alabama, and

the other stratum contains all the other centers combined. Table 11 illustrates that there are no apparent differences across centers at < 37 weeks and < 35 weeks gestation; however, at < 32 weeks there was a greater reduction of PTB in the 17OHP-C arm relative to vehicle at the University of Alabama compared to all other sites combined.

Table 11 Effect of Center on Proportion of Preterm Births at Weeks <37, <35, and <32

	University of Alabama			All Other Centers Combined			All Centers		
Data Source	17P[a] (n=86)	Vehicle (n=40)		17P[a] (n=224)	Vehicle (n=113)		17P[a] (n=310)	Vehicle (n=153)	
	%	%	% PTB decrease	%	%	% PTB decrease	%	%	% PTB decrease
<37 weeks	26.7	45.0	-18.3 %	41.1	58.4	-17.3 %	37.1	54.9	-17.8 %
<35 weeks	17.4	27.5	-10.1 %	22.8	31.9	-9.1 %	21.3	30.7	-9.4 %
<32 weeks	10.5	25.0	-14.5 %	12.5	17.7	-5.2 %	11.9	19.6	-7.7 %

Source: Response to FDA Question 1, 10/6/06

[a] Four 17P-treated patients were losses-to-follow-up. They are counted as deliveries at their gestational ages at time of last contact (18.6, 22.0, 34.4 and 36.6 weeks).

Medical Reviewer Comment

- *These findings support the conclusion that treatment with 17OHP-C had a significant effect on reducing PTBs <37 and <35 weeks. These findings, however, raise a concern about whether one study site had a disproportionate effect at <32 weeks.*

Other Secondary Efficacy Endpoints

Treatments/ Interventions in Pregnancy

The percentage of subjects who were given tocolytic agents during the study was similar in the two treatment groups (12.9% vs. 11.8%). The incidence of cerclage placement was also similar in both treatment groups (1.6% vs. 1.3%).

The incidence of cesarean section (C-section) in the 17OHP-C group was similar to that in the placebo group (25.2% vs. 26.8%). The most common reasons for a C-section in the 17OHP-C and placebo groups, respectively, were previous C-section (44.2% vs. 41.5%), abnormal presentation (23.4% vs. 29.3%), and fetal distress (14.3% vs. 19.5%).

Miscarriages, Stillbirths, and Neonatal Deaths

The incidences of miscarriages and stillbirths are summarized in (Table 12) and discussed in more detail in section 7.1.1. Five (1.6%) subjects, all in the 17OHP-C group (1.6%), experienced miscarriages. No subject in the placebo group miscarried.

The incidence of stillbirths was slightly higher in the 17OHP-C group, but the difference was not statistically significant. Eight subjects had stillbirths: 6 (2.0%) subjects in the 17OHP-C group and 2 (1.3%) subjects in the placebo group. Six of the eight stillbirths were antepartum stillbirths (fetal deaths in utero) and two occurred intrapartum.

The incidence of neonatal deaths was numerically twice as high in the placebo group (2.7% vs. 6.0%), but the difference was not statistically significant. If miscarriages and stillbirths are added to the neonatal deaths, the overall fetal and neonatal mortality was similar in the two treatment groups (6.2% in the 17OHP-C group vs. 7.2% in the placebo group).

Table 12 Miscarriages, Stillbirths, and Neonatal Deaths (Study 17P-CT-002)

Pregnancy Outcome	17OHP-C N=306 n (%) [A]	Vehicle N=153 n (%) [A]	Nominal P-value [B]
Miscarriages <20 weeks gestation	5 (1.6)	0	0.1746
Stillbirth	6 (2.0)	2 (1.3)	0.7245
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.1159
Total Deaths	**19 (6.2)**	**11 (7.2)**	**0.6887**

[A] Percentages are based on number of enrolled subjects and not adjusted for time on drug or at risk subjects in the respective gestational age.

[B] No adjustment for multiple comparisons.

Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

Medical Reviewer's Comment

- *The trend towards a benefit in the reduction of neonatal death in the 17OHP-C group is off-set by a trend toward an increase in the rates of miscarriage and possibly stillbirth associated with use of 17OHP-C, resulting in no net benefit regarding survival.*

Neonatal Outcomes

Neonatal Characteristics

Four hundred forty-six (446) live infants were delivered by 459 subjects with known delivery dates: 295 infants in the 17OHP-C group and 151 infants in the placebo group (Table 13).

Table 13 Neonatal Outcomes in Study 17P-CT-002

Neonatal Outcome	17OHP-C	Vehicle	Nominal P-value[A]
Number of subjects	310	153	--
Number of live births	295	151	--
Birthweight (g)			
Mean (SD)	2760 (859)	2582 (942)	0.0736
Min, Max	208, 4900	300, 4855	--
Birthweight <2500 g, n (%)	*82 (27.2)*	*62 (41.1)*	***0.0029***
Birthweight <1500 g, n (%)	26 (8.6)	21 (13.9)	0.0834
Head circumference			
Mean (SD)	32.5 (3.1)	32.0 (3.3)	0.0963
Min, Max	15.4, 37.5	21.5, 38.0	--
1 Minute Apgar			
Mean (SD)	7.5 (2.3)	7.3 (2.3)	0.2135
Min, Max	0, 9.0	0, 9.0	--
5 Minute Apgar			
Mean (SD)	8.3 (1.9)	8.3 (1.7)	0.1058
Min, Max	0, 10.0	0, 9.0	--
Major congenital malformation, n (%)	6 (2.0)	3 (2.0)	1.0000
Admitted to NICU or miscarriage/stillbirth/neonatal death, n (%)	93 (30.4)	57 (37.3)	0.1395
Admitted to NICU (live births), n (%)	*82 (27.8)*	*55 (36.4)*	***0.0434***
Days in NICU [B]			
Median	9.1	14.1	0.1283
Min, Max	0.1, 194.8	0.1, 147.0	--
Infant hospital days [C]			
Mean (SD)	8.7 (16.0)	13.3 (26.5)	0.3612
Min, Max	2, 123	2, 148	--

Birthweight and head circumference data were missing for some infants.

A: No adjustment for multiple comparisons

B: For neonatal deaths, days in the NICU were calculated until date of death. Days in NICU could not be determined for 3 patients in the 17OHP-C group and 2 patients in the placebo group.

C: Determined only for infants discharged alive.

Source: Table 11-7 Final Report for Study 17-CT-002.

Birthweight

The percentage of infants weighing <2500 g was statistically significantly lower in the 17OHP-C group than in the placebo group (27.2% vs. 41.1%). The percentage of infants weighing <1500 g also was numerically (but not statistically) lower in the 17OHP-C group (8.6% vs. 13.9%). There was no statistical difference between treatment groups in mean birthweight.

Apgar Scores
There were no differences between treatment groups in mean 1-minute and 5-minute Apgar scores.

Major Congenital Malformations
Nine (2.0%) infants overall had a major congenital malformation; the incidence rate was not different between treatment groups: 6 (2.0%) in the 17OHP-C group and 3 (2.0%) in the placebo group.

Admission to and Days in NICU
A smaller percentage of liveborn infants in the 17OHP-C group were admitted to the NICU compared with liveborn infants in the placebo group (27.8% vs. 36.4%). For live births, stay in the NICU ranged widely, from 0.1 - 194.8 days. The median stay in the NICU was numerically (but not statistically) shorter for the 17OHP-C group (9.1 vs. 14.1 days).

Hospital days were available for 285 infants in the 17OHP-C group and 140 infants in the vehicle group. The difference in mean hospital days between treatment groups was not statistically significant (8.7 (17OHP-C) vs. 13.3 days).

Neonatal Morbidity for Liveborn Infants
The incidences of use of supplemental oxygen (15.4% vs. 24.2%), any type of intraventricular hemorrhage (IVH) (1.4% vs. 5.3%), and necrotizing enterocolitis (NEC) (0% vs. 2.7%) were lower in the 17OHP-C group than the placebo group (see Table 14). However, the incidence of severe IVH (Grades 3 or 4) was numerically higher in the 17OHP-C group (0.7% vs. 0.0%).

The incidences of the following neonatal morbidities, while not statistically different between treatment groups, were lower in the 17OHP-C group: BPD (1.4% vs. 3.3%); patent ductus arteriosus (PDA) (2.4% vs. 5.4%); other intracranial hemorrhages (0.3% vs. 1.3%); and confirmed pneumonia (1.0% vs. 2.7%).

Composite neonatal morbidity/mortality was based on the number of neonates who died or experienced respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, proven sepsis, or necrotizing enterocolitis. The proportion of subjects who experienced the composite morbidity endpoint was numerically lower in the 17OHP-C group (11.9% vs. 17.2%), but the difference was not statistically significant.

Table 14 Neonatal Morbidity for Live Births

Morbidity	17OHP-C N=295 n (%)	Vehicle N=151 n (%)	Nominal P-value [A]
Transient tachypnea	11 (3.7)	11 (7.3)	0.0990
Respiratory distress syndrome (RDS)	29 (9.9)	23 (15.3)	0.0900
Bronchopulmonary dysplasia (BPD)	4 (1.4)	5 (3.3)	0.1730
Persistent pulmonary hypertension	2 (0.7)	1 (0.7)	1.0000
Ventilator support	26 (8.9)	22 (14.8)	0.0616
Supplemental oxygen	*45 (15.4)*	*36 (24.2)*	***0.0248***
Patent ductus arteriosus	7 (2.4)	8 (5.4)	0.1004
Seizures	3 (1.0)	0	0.5541
Any intraventricular hemorrhage (IVH)	*4 (1.4)*	*8 (5.3)*	***0.0258***
Grade 3 or 4 IVH	2 (0.7)	0	0.5511
Other intracranial hemorrhage	1 (0.3)	2 (1.3)	0.2628
Retinopathy of prematurity	5 (1.7)	5 (3.3)	0.3164
Proven newborn sepsis	9 (3.1)	4 (2.6)	1.0000
Confirmed pneumonia	3 (1.0)	4 (2.7)	0.2330
Necrotizing enterocolitis (NEC)	*0*	*4 (2.7)*	***0.0127***
Composite Neonatal Morbidity/Mortality [B]	*35 (11.9)*	*26 (17.2)*	*0.1194*

A: P-values have **not been adjusted** for multiple comparisons.

B: The *composite neonatal morbidity/mortality measure* counted any liveborn infant who experienced death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC.

Source: Table 11-8, Final Report for Study 17P-CT-002.

Medical Reviewer's Comments

- *The Applicant did not adjust for multiple comparisons. Without any adjustment, the incidences of use of supplemental oxygen (15.4% vs. 24.2%), any type of intraventricular hemorrhage (IVH) (1.4% vs. 5.3%), and necrotizing enterocolitis (NEC) (0% vs. 2.7%) were statistically lower in the 17OHP-C group than the placebo group. However, had such an adjustment been performed, it is unlikely that any of the listed morbidities would have been statistically lower in the 17OHP-C treatment group in this clinical trial.*

- *The composite neonatal morbidity score included neonatal death and the major morbid conditions of the neonate. Although the composite neonatal morbidity score was numerically lower in the 17OHP-C treatment group (11.9% vs. 17.2%), the difference did not reach statistical significance. This is not surprising considering that the study was not powered to demonstrate a reduction in morbidity or mortality.*

Study 17P-IF-001 (Supportive Clinical Trial)

Subject disposition

A total of 150 subjects were randomized, 94 to 17OHP-C and 56 to placebo. One hundred four (104) subjects (65 randomized to 17OHP-C and 39 randomized to vehicle) had ended their treatment prior to the study termination either because they had completed treatment with study drugs through 36^6 weeks or delivery or had terminated treatment prematurely for reasons other than recall of study drugs. Fifty-seven (61%) of subjects in the 17OHP-C group and 29 (52%) in the placebo group completed treatment through 36^6 weeks or delivery.

Among the subjects not impacted by recall of study drug, the reasons for not completing treatment in the 17OHP-C group were adverse event (n = 1), withdrawal for non-clinical reasons (n = 6), and lost to follow up (n = 1). The reasons for not completing treatment in the placebo group were adverse event (n = 2), withdrawal for non-clinical reasons (n = 6), and lost to follow up (n = 2).

Primary Efficacy Outcome

The incidence of delivery <37 weeks gestation for (1) the intent-to-treat (ITT) population, (2) the population for which data were available (all subjects other than those lost to follow up), and (3) those subjects whose treatment was not prematurely terminated because of recall of study drug are listed in Table 15 For each analysis population, the percentage of subjects with a delivery of <37 weeks gestation was numerically higher in the 17OHP-C treatment group. None of the differences were statistically different.

Table 15 Percentage of Subjects with Delivery <37 Weeks Gestation

Analysis Population	17OHP-C		Vehicle	
	N	n (%)	N	n (%)
ITT population	94	39 (41.5)	56	20 (35.7)
All available data	93	38 (40.9)	54	18 (33.3)
Not withdrawn due to study termination	**65**	**28 (43.1)**	**39**	**15 (38.5)**

ITT population was all randomized subjects. Subjects with missing outcome data were classified as having a preterm birth <37 weeks (treatment failure).

Source: Table 9-3, pg 21, abbreviated Final Report for Study 17P-IF-001.

Medical Reviewer's Comment

- *The data obtained from the analysis population identified as "not withdrawn due to study termination" is of most value since all subjects in this population had the opportunity to complete a full course of treatment. However, because the potency and overall quality of the study drugs could not be assured, the efficacy data obtained from this prematurely terminated clinical trial is of limited value and must be interpreted with caution.*
- *The findings from this trial do not suggest any benefit of 17OHP-C in reducing the percentage of subjects with a delivery <37 weeks gestation.*

- *In the "not withdrawn due to study termination" analysis population, the percentage of subjects with a delivery <37 weeks gestation was 38.5% in the placebo group. This rate of premature birth is close to that which the MFMU Network used in their sample size calculations for both this study and study 17P-CT-002. The percentage of subjects with a delivery <37 weeks gestation in the placebo group of Study 17P-CT-002, however, was considerably higher, namely, 54.9%. The difference in the rates of premature birth in the placebo arms of the 2 clinical trials (38.5% vs. 54.9%) was not expected, since both studies were conducted at the same clinical sites in close temporal proximity.*

Secondary Efficacy Outcomes

Miscarriages, Stillbirths, and Neonatal Deaths

The number and percentages of miscarriages, stillbirths, and neonatal deaths in the ITT population are listed by treatment group in Table 16.

Table 16 Number of Miscarriages, Stillbirths, and Neonatal Deaths (Study 17P-IF-001)

Fetal/Neonatal Deaths	17OHP-C N=93	Vehicle N=54
Miscarriages	1 (1.1)	1 (1.9)
Stillbirths	1 (1.1)	2 (3.7)
Neonatal deaths	2 (2.2)	0
Total	**4 (4.4)**	**3 (5.9)**

Source: Table 9-8, pg 28, abbreviated Final Report for Study 17P-IF-001.

Medical Reviewer's Comment

- *Although this study did not demonstrate any overall benefit for treatment with 17OHP-C in terms of reduction in overall mortality, there was no trend toward an increased rate of miscarriages in the 17OHP-C group as was seen in Study 17P-CT-002.*

6.1.5 Clinical Microbiology

Not applicable because the product is not an antimicrobial.

6.1.6 Efficacy Conclusions

The results from Study 17P-CT-002 of 463 pregnant subjects with a history of prior spontaneous preterm deliveries show the following:

- The frequency of preterm birth <37 weeks gestation was statistically significantly decreased in the 17OHP-C treatment group compared to that in the placebo group (37.1% vs. 54.9%). The reduction in preterm birth <37 weeks was independent of race, number of qualifying preterm births, and gestational age of the qualifying preterm birth.

- The frequency of preterm births <35 weeks (point estimate of -9.4%, 95% CI [-18.7%, -0.2%]) and <32 (point estimate of -7.7%, 95% CI [-16.1.%, -0.3%]weeks gestation was statistically decreased in the 17OHP-C arm.
- There is consistency of PTB reduction across centers at <37 weeks and <35 weeks gestation; however, at <32 weeks there was a greater reduction of PTB in the 17OHP-C arm at the University of Alabama compared to all other sites combined.
- The prolongation of pregnancy, defined as the time from randomization to delivery or date last pregnant, was numerically longer, by a mean of 6 days, in the 17OHP-C group compared to the placebo group. The mean gestational age at delivery was one week greater in the 17OHP-C group compared to the placebo group (36.2 vs. 35.2 weeks); this was statistically significant at p=.031.
- Neonatal mortality was numerically lower in the 17OHP-C group, but the between-group difference was not statistically significant (2.6% vs. 5.9%).
- Overall mortality (fetal and neonatal combined) was similar across the 2 treatment groups (19 of 306 [6.2%] in the 17OHP-C group vs. 11 of 153 [7.2%] in the vehicle group).
- Composite neonatal morbidity (neonates with death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC) was numerically lower in the 17OHP-C group, but the between-group difference was not statistically significant (11.9 vs. 17.2).
- The percentage of infants weighing <2500 g was statistically lower in the 17OHP-C group compared with the placebo group (27.2% vs. 41.1%). The percentage of infants weighing <1500 g was numerically lower in the 17OHP-C group (8.6% vs. 13.9%) but not statistically different.
- Use of tocolytic therapy and cerclage placement were not significantly different between the 17OHP-C and placebo groups.

Medical Reviewer's Comments

- *It is important to note that the statistically significant reduction in preterm birth <37 weeks was independent of race, number of qualifying preterm births, and gestational age of the qualifying preterm birth. This generalizability increases the likely clinical significance of this finding and the usefulness of this drug.*
- *The Division was particularly interested in the preterm birth rate at gestational ages < 35 weeks and <32 weeks gestation since these lower gestational ages correlate more closely with infant mortality or morbidity. The percentages of preterm births at these gestational ages in the 17OHP-C arm were statistically lower than those in the vehicle arm. The upper bound of the 95% confidence intervals (after adjustment for the interim analyses) did not cross zero, meeting the usual criteria for statistical significance. However, the level of statistical significance was not of the level that one would like to observe for an Application containing only a single clinical trial.*
- *The lack of consistency of PTB reduction at <32 weeks across all sites is of concern.*

- *The composite neonatal morbidity/mortality index (non-surrogate endpoint), was numerically lower in the 17OHP-C group but this finding was not statistically significant. However, this was a post hoc analysis requested by the FDA and the study was not powered for this endpoint.*
- *The strength of the efficacy data relies on statistical significant reductions of PTB at <35 and <32 weeks gestation, surrogate endpoints which are thought by the advisory committee to predict reduction in neonatal mortality and morbidity. The results of studies in the literature (see section 8.6) provide further support for the effectiveness of 17OHP-C for prevention of PTB; however, the small size and variable entry criteria for these studies limit the strength of their findings.*
- *The major weakness of the this data is that it relies on a single multicenter study, with a possible inconsistency across sites.*

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Studies 17P-IF-001 and 17P-CT-002 were conducted under an IND, but adverse events (AEs) were not captured in the typical manner used in studies designed to support drug approval. Assessment of severity or relationship of AEs to study drug was not made for non-serious AEs. Adverse events that were considered serious or unexpected by the investigator were reported using the MFMU Network AE Form, which requested assessments of severity and relationship to study drug. Since the potency of the recalled drug in study 17P-IF-001 was in question, the safety findings are described separately for study 17P-CT-002 and study 17P-IF-001 unless otherwise indicated.

Medical Reviewer's Comment

- *Although adverse events were not captured in the typical manner, this reviewer does not think that the application was significantly compromised by this. Although it is customary to ask investigators to assess severity of an AE or the relationship to the study drug, FDA reviewer's tend to make their own independent assessments. Serious or unexpected AEs are most important and these were collected.*

7.1.1 Deaths

Maternal
There were no maternal deaths in the trial.

Miscarriages, Stillbirths, and Neonatal deaths
Miscarriage (spontaneous abortion) is the loss of the products of conception from the uterus before the fetus is viable (< 20 weeks gestation). Stillbirth is the delivery of a dead infant (≥ 20 weeks gestation). There was a higher incidence of miscarriage and stillbirth in the

17OHP-C group (11 of 306 subjects [3.5%] vs. 2 of 153 subjects [1.3%]), but a lower incidence of neonatal deaths (8 of 306 subjects [2.6%] vs. 9 of 153 subjects [5.9%]). Neither of the between-group differences was statistically significant.

Miscarriages

Five of 306 (1.6%) subjects randomized to 17OHP-C had miscarriages, compared with no subjects randomized to placebo. Another 17OHP-C subject (subject 004-035) had a spontaneous vaginal delivery of a nonviable fetus at 20^{1} weeks gestation, which was classified as a neonatal death; the infant had 1- and 5-minute Apgar scores of 1 and died the day of delivery due to extreme prematurity.

Two of the five subjects who had miscarriages had a clinical diagnosis of chorioamnionitis at the time of the miscarriage. Subject 008-114 miscarried after her 3rd injection of 17OHP-C at 19^{1} weeks gestation. Subject 015-023 had a previous stillbirth, a previous miscarriage, and had a miscarriage on the day of her 2nd 17OHP-C injection at 19^{1} weeks gestation.

Subject 015-014 had a previous stillbirth, and during this pregnancy had bacterial vaginosis prior to randomization. She received 3 injections of 17OHP-C before experiencing preterm premature rupture of the membranes (pPROM) at 18^{6} weeks gestation. She chose to terminate the pregnancy due to a poor prognosis for the infant. Although classified as an induced abortion on the AE form, the event was entered in the database as a miscarriage.

One subject (subject 008-110) smoked a pack a day of cigarettes and used cocaine during the study pregnancy. After receiving a single injection of 17OHP-C, she experienced a miscarriage at 18^{2} weeks gestation.

Only one of the five subjects who had a miscarriage had no identifiable factor that might have contributed to the miscarriage. However, prior to entering the study, this subject (subject 004-048) had an emergency room visit for a threatened abortion at 9^{4} weeks gestation. She was randomized to 17OHP-C at 17^{3} weeks gestation and received her only injection of 17OHP-C on that day. Five days later, she experienced pPROM and had a spontaneous vaginal delivery of a nonviable infant.

Medical Reviewer's Comments

- *The Applicant notes that infection appears more likely to be contributory to miscarriage than does exposure to 17OHP-C. The rate of chorioamnionitis and vaginitis in subjects treated with vehicle (none of whom miscarried) was not significantly lower; however, although there is no data in humans, animal studies suggest the possibility that 17OHP-C could contribute to sub-clinical infection.*
- *Data on second trimester miscarriage rates also are available from four studies reported in a meta-analysis of published studies.[28] Data in the meta-analysis publication showed a possible trend toward an increased risk of miscarriage in the 17OHP-C arms of the four studies as compared to placebo, but the trend did not approach statistical significance (odds ratio of 1.30, with 95% confidence interval of 0.61 – 2.74).*

- *The results of the current clinical trial, in conjunction with the meta-analysis cited above, demonstrated a trend toward increased second trimester miscarriage seen with the use of 17OHP-C and these findings should be investigated further in a clinical trial.*

Stillbirths

There were a total of eight stillbirths, six occurring in the 17OHP-C group and two in the placebo group. The difference in incidence of stillbirths was not statistically significant (2.0% for 17OHP-C vs. 1.3% for placebo).

Two of the stillbirths, one in each treatment group, occurred intrapartum. Neither subject had a prior stillbirth. Subject 023-007 started 17OHP-C at 18^{5} weeks gestation of her 4th pregnancy and received 3 injections with no AEs. She had nothing in her obstetrical history that could explain the stillbirth at 21^{0} weeks gestation. Subject 008-060 started placebo at 18^{4} weeks gestation. She had bacterial vaginosis prior to randomization. She received five injections of placebo with no AEs, and then developed preeclampsia at 23^{6} weeks gestation with symptoms consistent with placental abruption. Labor was induced and a stillborn fetus was delivered.

Six of the stillbirths occurred as fetal deaths in-utero (five in the 17OHP-C arm; one in the placebo arm). Three 17OHP-C subjects (008-102, 015-022, and 017-011) had bacterial vaginosis or Trichomonas vaginalis during the study pregnancy prior to randomization. Subject 014-012 in the 17OHP-C group had a clinical diagnosis of chorioamnionitis during the pregnancy. These infections may have played some role in causing the stillbirths. Subject 018-024 in the 17OHP-C group had no identifiable factor in her obstetrical history or study data that could have contributed to the stillbirth. The vehicle subject (subject 013-005) had a urinary tract infection before randomization and was a smoker (10 cigarettes/day).

Medical Reviewer's Comments

- *The total numbers of stillbirths were small; however, the proportion of stillbirths in the 17OHP-C arm (2.0% [6 of 306 subjects]) was numerically, but not statistically higher than the vehicle arm (1.3% [2 of 153 subjects]). All stillbirths for whom a risk was identified (seven out of eight) were associated with a potential predisposing infectious process: e.g. bacterial vaginosis, urinary tract infection, chorioamnionitis.*
- *There was no difference in possible factors predisposing to fetal loss (e.g. bacterial vaginosis, chorioamnionitis) between the two arms of this study.*
- *A difference in subclinical infection/inflammation between the two arms is not known.*

Neonatal Deaths

The incidence of neonatal death was twice as high in the placebo group, with nine deaths (5.9% of births) occurring in the placebo group, as compared to eight in the 17OHP-C group (2.6% of births). This did not reach statistical significance. The gestational ages at delivery of these infants ranged from 20^{3} to 28^{1} weeks in the placebo group and from 20^{1} to 35^{1} weeks in the 17OHP-C group. The neonatal death in the 35-week delivery in the 17OHP-C group occurred in an infant delivered by emergency cesarean section following uterine rupture. Excluding this

infant, the gestational age at the time of the delivery of the neonatal deaths was similar between groups.

Medical Reviewer's Comment

- *The similar gestational ages at delivery of the neonatal deaths in the two groups suggests that the gestational age-adjusted neonatal death rate would be similar for each group. This further suggests that the decreased neonatal death rate in the 17OHP-C group is attributable to a lower proportion of early preterm deliveries, rather than a difference in the condition of the delivered neonates.*

7.1.2 Other Serious Adverse Events

Congenital Anomalies (Reported as Adverse Events)

The incidence of congenital malformations was 2% in both treatment groups. The six cases in the 17OHP-C group included two congenital genitourinary anomalies (a male with obstructive defects of the renal pelvis and ureter and a female with a hydrocele of the tunica vaginalis), two infants with congenital cardiovascular anomalies (cardiomegaly/left ventricular diverticulum/ pericardial defect and one reported as "other anomalies of the circulatory system"), one infant with polydactyly and talipes calcaneovarus and one with congenital flat feet. The three cases in the placebo group were an infant with a congenital cardiovascular anomaly (stenosis and other anomalies of the circulatory system) and polydactyly, one with a congenital genitourinary anomaly (anomalies of the bladder and urethra), and one with talipes equinovarus.

Medical Reviewer's Comment

- *The number and type of congenital anomalies appear evenly distributed over the treatment arms. This rate of anomalies is consistent with the background rate for congenital anomalies in the general population of 2-3%.*

Non-Fatal Serious Adverse Event Reports (SAEs)

Three subjects, all of whom received 17OHP-C, and an infant whose mother was in the 17OHP-C arm had non-fatal SAEs that triggered the submission of a serious unexpected adverse event report.

Patient 002-026 had a pulmonary embolus after delivery. The subject was randomized to 17OHP-C at 19^4 weeks gestation and received 17 injections of 17OHP-C before delivery. She had a labor visit between the 8^{th} and 9^{th} injections and again between the 15^{th} and 16^{th} injections of study drug. She experienced significant antepartum bleeding during the second labor visit and had a positive lupus anti-coagulant test, but continued in the study. She had no symptoms of thromboembolic events during the pregnancy. Eight days after delivery at 36^4 weeks, the subject experienced a pulmonary embolus, which was successfully treated and did not result in any sequelae.

Patient 013-021 reported a knot at the injection site on her right hip, which was very sore, after the 8th injection of 17P. She was diagnosed with cellulitis and started on penicillin. The subject requested to remain in the study and had a spontaneous PTD at 31^4 weeks gestation.

Patient 014-012 had a stillbirth at 21^{1} weeks gestation, and developed postpartum hemorrhage and respiratory distress after delivery. The subject was intubated and given multiple transfusions of red blood cells before being discharged to specialty care. The subject continued on antibiotics for endometritis and excessive surgical manipulation.

Patient 017-016 delivered a male infant at 37^{5} weeks gestation with small penis and testes. An ultrasound of the scrotum revealed infarcted testicles secondary to intrauterine torsion. Human chorionic gonadotropin, congenital hypothyroidism, and follicle stimulating hormone, and chromosome testing were done and found to be normal. The infant was diagnosed as possibly having hypogonadism.

Medical Officer's Comment

- *A causal association of these four maternal serious AEs with exposure to 17OHP-C is unlikely.*

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The rate of early discontinuations from treatment with study drug due to AEs was comparable in the two treatment groups, and the AEs leading to discontinuation were not notably different. Seven (2.2%) subjects in the 17OHP-C group and four (2.6%) subjects in the vehicle group either discontinued or were withdrawn by the investigator from study drug due to AEs (Table 17).

7.1.3.2 Adverse events associated with dropouts (withdrawal due to adverse event).

The principal AEs that led to discontinuation from treatment in the 17OHP-C and vehicle groups are listed by subject in Table 17:

Table 17 Adverse Events Leading to Treatment Discontinuation (Study 17P-CT-002)

Patient ID	Treatment Group	Adverse Event	Gestational Age at Discontinuation
002-024	17OHP-C	Urticaria	23.3 weeks
004-018	17OHP-C	Soreness at injection site	23.3 weeks
011-027	17OHP-C	Arthralgia/Severe Joint Pain	19.6 weeks
019-015	17OHP-C	Urticaria	31.1 weeks
020-026	17OHP-C	Weight Gain	26.3 weeks
020-044	17OHP-C	Urticaria	24.3 weeks
020-060	17OHP-C	Red welt at injection site	20.5 weeks
025-001	Vehicle	Pruritus	34.3 weeks
008-055	Vehicle	Pruritus (head to toe)	20.1 weeks
015-033	Vehicle	Swelling at injection site/Pruritus	30.6 weeks
018-018	Vehicle	Urticaria	26.1 weeks

Source: Section 16.2, Listing 7.5, Final Report for Study 17P-CT-002

Another subject in the 17OHP-C group was listed as being withdrawn early by the investigator due to pPROM, which was not considered an AE in this study. Four subjects in the 17OHP-C group were lost to follow up, and one of these four subjects reported swelling at the injection site at the last two visits before being lost to follow up. The other three subjects who were lost to follow up had no AEs reported.

A vehicle treated subject was also withdrawn early by the investigator due to pPROM.

Twenty-eight (28) other subjects discontinued study drug early due to "non-clinical reasons" according to the applicant's classification: 19 in the 17OHP-C group and nine in the vehicle group. No other information was provided on the CRF as to why the subject discontinued. Of the 19 subjects in the 17OHP-C group, 12 had no recorded AEs. Of the remaining seven subjects, four had AEs within 2 visits of discontinuation, and therefore, without additional information as to the reason for discontinuation, the role of an AE in the decision to discontinue can not be excluded. The AEs reported by these subjects prior to discontinuation were injection site reactions (n=3) and diarrhea, vomiting, and loss of appetite (n=1 for each). Of the nine subjects in the vehicle group who discontinued for non-clinical reasons, six had no recorded AEs.

Medical Reviewer's Comment

- *The Applicant computed a worst-case scenario by adding the five 17OHP-C subjects and the one vehicle subject who had experienced AEs shortly before discontinuation/loss to follow-up to the group of subjects who discontinued due to AEs. By this conservative estimate of the incidence of discontinuation due to AEs, the incidence is still similar between the treatment groups (3.9% vs. 3.3%).*

- *The majority of AEs that clearly or possibly led to early discontinuation were injection site reactions, which occurred with both 17OHP-C and vehicle treatments. Two subjects, one in each treatment group, had possible allergic reactions, which have been reported previously for 17OHP-C.*
- *The adverse events that were associated with premature termination of treatment do not raise any concerns about the safety of 17OHP-C for the prevention of preterm birth.*

7.1.3.3 Other significant adverse events

No other significant adverse events that have not been reported elsewhere were identified.

7.1.4 Other Search Strategies

See section 8.6 for a review of the literature.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

This study was conducted under an IND, but adverse events (AEs) were not captured in the typical manner used for studies designed to support a drug application. During this study, Investigators were not required to provide an assessment of severity or relationship to study drug for each non-serious adverse event. Adverse events that were considered serious and unexpected by the Investigator were reported using the MFMU Network AE Form, which requested assessments of severity and relationship to study drug, rather than the study CRF. The AEs reported on the MFMU Network AE Form were entered into the study database and included in the listings and summaries of all AEs.

Medical Reviewer's Comment

- *Although adverse events were not captured in the typical manner, this reviewer does not think that the application was significantly compromised by this. Although it is customary to ask investigators to assess severity of an AE or the relationship to the study drug, FDA reviewer's tend to make their own independent assessments. Serious or unexpected AEs are most important and these were collected.*

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The maternal adverse events, miscarriages, stillbirths, neonatal deaths, and neonatal congenital anomalies were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 8.0 and summarized by system organ class, higher level term, and preferred term.

7.1.5.3 Incidence of common adverse events

The most common AEs in both treatment groups were injection site reactions (which included pain, swelling, pruritus), reported by 42.3% of 17OHP-C subjects and 38.6% of placebo subjects. The types of injection site reactions did not differ between the treatment groups, except for injection site swelling, which occurred with a significantly greater incidence in the 17OHP-C group compared with the placebo group (17.1% vs. 7.8%).

Infections were not recorded as AEs during the study, but were captured indirectly if they resulted in antibiotic use. The incidence of any vaginal/cervical infection was greater in the 17OHP-C group (21.6%) as compared to the placebo group (15%). Incidences in the 17OHP-C and placebo groups, respectively, of bacterial vaginosis (8.7% vs. 5.2%) and trichomonas (3.9% vs. 1.3%) did not differ significantly.

7.1.5.4 Common adverse event tables

Adverse events by preferred terms that occurred in >2% of subjects in either treatment group are shown in Table 18. The most common adverse events (and the percentage of subjects reporting them in the 17OHP-C group in decreasing order of frequency were injection site pain (34.8%), injection site swelling (17.1%), urticaria (12.3%), pruritus (7.7%), injection site pruritus (5.8%), nausea (5.8%), and contusion (5.5%). The most common adverse events (and the percentage of subjects reporting them in the vehicle group in decreasing order of frequency were injection site pain (32.7%), urticaria (11.1%), contusion (9.2%), injection site swelling (7.8%), pruritus (5.9%), and neonatal death (5.9%).

Table 18 Adverse Events that Occurred in >2% of Subjects in either Treatment Group

Preferred Term [A]	17OHP-C N=310 n (%)	Vehicle N=153 n (%)
Injection site pain	108 (34.8)	50 (32.7)
Injection site swelling [B]	53 (17.1)	12 (7.8)
Urticaria	38 (12.3)	17 (11.1)
Pruritus	24 (7.7)	9 (5.9)
Injection site pruritus	18 (5.8)	5 (3.3)
Nausea	18 (5.8)	7 (4.6)
Contusion	17 (5.5)	14 (9.2)
Injection site nodule	14 (4.5)	3 (2.0)
Vomiting	10 (3.2)	5 (3.3)
Death [C, D]	8 (2.6)	9 (5.9)
Anorexia	5 (1.6)	6 (3.9)
Injection site irritation	4 (1.3)	5 (3.3)
Abdominal pain	3 (1.0)	4 (2.6)

[A] Patients reporting a particular AE more than once were counted only once for that AE. AEs were coded using MedDRA Version 8.0.
[B] Incidence in 17OHP-C group was significantly higher (p>0.05) than placebo group, based on a chi-square test.
[C] Death included only neonatal deaths.
[D] For safety assessments, the incidence of neonatal death was based on all randomized patients, so the percentages are slightly lower than those reported for the efficacy assessment based on liveborn infants.
Source: Table 12-2, Final Report for Study 17-CT-002.

Medical Reviewer's Comment

- *The number (percentages) of the specific adverse events listed in Table 18 differ slightly from those presented in the narrative in Section 7.1.5.3. In Section 7.1.5.3, adverse events have been combined into higher levels terms (e.g., injection site reaction) or were obtained indirectly (e.g., use of antibiotics to signify and infection).*
- *The majority of all adverse events were related to injection site reactions. Further research into other forms of administration or the use of other vehicles may be useful.*
- *Infections are not listed on the table because they were captured indirectly through antibiotic use. This is not an ideal way of evaluating infection. Specific assessments of infections would be useful since there is a difference in which infections are associated with preterm birth. However, the most significant risk of infection is apparently sub-clinical, which would not be captured in a practical manner in this type of clinical trial.*

7.1.5.5 Identifying common and drug-related adverse events

The most common maternal drug related adverse events identified were related to injection site reactions. Injection site pain was the most commonly reported adverse event, affecting a third

of subjects in each arm. Injection site swelling was the next most common adverse event, followed by urticaria, pruritus, and injection site pruritus. Other possible drug related maternal adverse events may be pregnancy related such as diabetes, preeclampsia or oligohydramnios. Possible fetal/neonatal drug related adverse events were a potential increase in fetal wastage.

Medical Reviewer's Comments

- *The only adverse events that were identified to be clearly attributed to this drug are injection site reactions. Further studies are needed to clarify what the relationship is, if any, between this drug and the complications of pregnancy or fetal wastage mentioned above.*

7.1.5.6 Additional analyses and explorations

This reviewer requested that the Applicant provide the total number of subjects who received the "screening" injection without enrolling in the study, and further detail the number/percent who experienced injection site reactions and the number/percent who subsequently declined enrollment into the study due to injection site reactions. This information is provided for study 17P-CT-002 in Table 19 and for study 17P-IF-001 in Table 20. "Injection site reaction" was not a choice on the case report form (CRF); instead, "clinical/perceived side effects" was a choice but was not recorded as the reason for any subject not being randomized. In study 17P-CT-002, 33 of 506 subjects (8.5%) receiving the screening injection did not continue with the study. In study 17P-IF-001, 10 of 160 subjects (6.2%) receiving the screening injection did not continue with the study.

Table 19 Disposition of Subjects Receiving a Trial Injection – Study 17P-CT-002

	Total Receiving trial injection (N=506)
Randomized	463 (91.5%)
GA >20,6 weeks	1 (0.2%)
Cervical Cerclage	2 (0.4%)
Hypertension requiring medication	1 (0.2%)
Cannot arrange randomization visit<=20,6 weeks	3 (0.6%)
Delivery/prenatal care elsewhere	1 (0.2%)
No show/withdrew consent	23 (4.6%)
Qualifying delivery does not meet criteria	2 (0.4%)
Delivery	2 (0.4%)
Study recruitment ended	8 (1.6%)

Source: Applicant's response to FDA request, 22 August 2006.

Table 20 Disposition of Subjects Receiving a Trial Injection – Study 17P-IF-001

	Total Receiving trial injection (N=160)
Randomized	150 (93.8%)
Cannot arrange randomization visit<=20,6 weeks	2 (1.3%)
No show/withdrew consent	6 (3.8%)
Protocol Suspension	2 (1.3%)

Source: Applicant's response to FDA request, 22 August 2006

Medical Reviewer's Comments

- *For 23 out of 506 subjects or 4.6% receiving the trial injection in study 17P-CT-002 who did not continue into treatment, the reason for not receiving treatment was "no show/withdrew consent." Since this population demonstrated high motivation to participate in this study, it is the opinion of this reviewer that most of these 23 subjects (4.6%) were not willing to be subjected to the injection. Considering the significance of this clinical problem and the resulting high motivation of subjects in preterm labor trials, this number is fairly high in the opinion of this reviewer.*
- *For 6 out of 160 subjects or 3.8% receiving the trial injection in study 17P-IF-001 who did not continue into treatment, the reason was "no show/ withdrew consent." The same comments as above apply here also.*
- *The applicant should explore the possibility of using other vehicle preparations which may be less irritating and lead to greater patient acceptability.*

Pregnancy Complications and Maternal Outcomes

The incidence of maternal pregnancy complications (gestational diabetes, oligohydramnios, significant antepartum bleeding, preeclampsia/gestational hypertension, abruption, confirmed clinical diagnosis of chorioamnionitis, or cerclage placement) did not differ significantly between the treatment groups (Table 21). The most common pregnancy complications (>5% of subjects in either treatment group) were preeclampsia or gestational hypertension (8.8% [17OHP-C group] vs. 4.6%) and gestational diabetes (5.6% [17OHP-C group] vs. 4.6%).

Overall, 70 subjects were admitted for preterm labor (PTL), other than the delivery admission, with similar rates in the two treatment groups: 16.0% of 17OHP-C subjects and 13.8% of vehicle subjects. The mean length of hospital stay for the mothers for PTL was not different between the treatment groups (3.1 vs. 3.7 days).

Table 21 Pregnancy Complications – Study 17P-CT-002

Complication or Outcome	17OHP-C N=306 n (%)	Vehicle N=152 n (%)
Hospital or labor/delivery admission for PTL* (other than the delivery admission)	49 (16.0)	21 (13.8)
Gestational diabetes	17 (5.6)	7 (4.6)
Oligohydramnios	11 (3.6)	2 (1.3)
Significant antepartum bleeding	6 (2.0)	3 (2.0)
Preeclampsia or gestational hypertension	27 (8.8)	7 (4.6)
Abruption	5 (1.6)	4 (2.6)
Confirmed clinical chorioamnionitis	11 (3.6)	5 (3.3)
Cerclage placement	5 (1.6)	2 (1.3)
Other complication	8 (2.7)	5 (3.3)

* PTL = preterm labor
Source: Table 12-3 Final Report for Study 17-CT-002.

Medical Reviewer's Comment

- *When looking at **both study 17P-CT-002 and 17P-IF-001**, this reviewer noted that three out of the nine complications of pregnancy reported by the Applicant occurred in a greater percentage of subjects in the 17OHP-C arm. The pregnancy complications were gestational diabetes, oligohydramnios, and preeclampsia. The numbers of subjects with these complications in both the principal study, 17P-CT-002 and the initial formulation study, 17P-IF-001, are listed in Table 22 below.*

There was a small numerical increase in the percentage of subjects with gestational diabetes in the 17OHP-C arm in the principal study. In the initial formulation study (IF-001), there were eight cases of gestational diabetes in the 17OHP-C arm compared to no cases in the vehicle arm. This difference approached statistical significance.

In terms of oligohydramnios, there was almost a three-fold increase in the percentage of subjects with oligohydramnios in the 17OHP-C arm of the principal study although the actual percent difference was small (3.6% vs. 1.3%).

The percentage of subjects with preeclampsia in the 17OHP-C arm in the principal study was almost twice that in the vehicle arm. The percentage of subjects with preeclampsia in the 17OHP-C arm in the initial formulation study was also higher.

Table 22 Selected Pregnancy Complications: Studies 17P-CT-002 and 17P-IF-001

Pregnancy Complication	Study	17OHP-C N (%)	Vehicle N (%)
Gestational Diabetes	CT- 002	17 (5.6)	7 (4.6)
	IF- 001	8 (8.6)	0 (0.0)
Oligohydramnios	CT- 002	11 (3.6)	2 (1.3)
	IF- 001	2 (2.2)	1 (1.9)
Preeclampsia	CT- 002	27 (8.8)	7 (4.6)
	IF- 001	6 (6.5)	2 (3.8)

Source: Adapted from table 12-3 Final Report for Study 17-CT-002.

Medical Reviewer's Comment

- *The mean gestational age at the time of diagnosis of preeclampsia in the 17OHP-C arm of study 17P-CT-002 was 35.6 weeks compared to 33.9 weeks in the vehicle arm. The higher gestational age at birth of subjects in the 17OHP-C arm could explain, in part, why there was a numerically higher percentage of preeclampsia in that arm, as the incidence rises with increasing gestational age.*

7.1.6 Less Common Adverse Events

Due to the size of the data base, and the manner in which adverse events were collected, an accurate assessment of less common adverse events cannot be determined in a meaningful way.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

No samples for laboratory tests were analyzed specifically as part of this study. All subjects, however, received prenatal care, and all routine labs associated with such care were performed and analyzed. Clinical situations that warranted the delivery of the subject or any other medical interventions were acted on by the managing clinicians.

Medical Reviewer's Comments

- *This reviewer does not think that the absence of collecting laboratory data specifically for the purpose of these clinical trials raises a safety concern regarding approvability of 17OHP-C. The presence of such study related laboratory data would not likely assist in making the decision whether or not to approve this drug. The 1979 Delalutin label mentions the following laboratory alterations:*
  1. *Inhibition of gonadotropic hormones – not relevant in pregnant patients*
  2. *Alteration of hepatic function (no specific information provided): patients with chronic liver disease will not likely be given drugs to prevent preterm birth.*

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

No samples for laboratory tests were analyzed specifically as part of this study. See Section **7.1.7.1.**

7.1.7.3 Standard analyses and explorations of laboratory data

No samples for laboratory tests were analyzed specifically as part of this study, See Section **7.1.7.1.**

7.1.7.4 Additional analyses and explorations

No samples for laboratory tests were analyzed specifically as part of this study. See Section **7.1.7.1.**

7.1.7.5 Special assessments

No samples for laboratory tests were analyzed specifically as part of this study. See Section **7.1.7.1.**

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were done as part of routine prenatal care but were not part of the clinical trial. However, vital sign data were not submitted as part of the clinical trial database.

Medical Reviewer's Comment

- *This reviewer thinks that vital sign data may have been helpful to refine dosing and provide direction to optimize therapy. However, the lack of routine vital sign data does not preclude a decision for approval based on efficacy or safety of this drug. Illnesses with significant vital sign changes such as preeclampsia were reported (see Table 21). Significant vital sign changes that warranted delivery of the patient or any other medical interventions were acted on by the managing clinician.*

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital signs were done as part of routine prenatal care but were not part of the clinical trial. See Section **7.1.8.1.**

7.1.8.3 Standard analyses and explorations of vital signs data

Vital signs were done as part of routine prenatal care but were not part of the clinical trial. See Section **7.1.8.1.**

7.1.8.4 Additional analyses and explorations

Vital signs were done as part of routine prenatal care but were not part of the clinical trial. See Section **7.1.8.1.**

7.1.9 Electrocardiograms (ECGs)

ECGs were not performed as part of this study.

Medical Reviewer's Comment

- *Pregnant women generally represent a young and relatively healthy population. ECGs are not performed as part of routine prenatal care; however, they are warranted in patients with hypertension requiring medication or in many congenital heart conditions. Women with these conditions were excluded from the study.*

7.1.10 Immunogenicity

Immunogenicity data was not collected as part of this study.

Medical Reviewer's Comment

- *No studies to assess immunogenicity were planned as part of this study and none were requested. Allergic reactions occurred in a small number of subjects and are expected in some individuals who use any "non-self" product. Based on data in the AERS database, there is no signal that 17OHP-C is likely to be responsible for allergic adverse events beyond that associated with other approved progestins.*

7.1.11 Human Carcinogenicity

Collecting this data was not part of the clinical trial.

Medical Reviewer's Comments

- *This reviewer recommends that the applicant collect data on carcinogenicity in the offspring of mothers exposed to this drug as part of a registry.*

7.1.12 Special Safety Studies

Study 17P-FU (Follow-up Safety Study)

Description of the Protocol

Infants born to women enrolled in Study 17P-CT-002, and who survived to be discharged from the nursery, were eligible for participation in the follow-up safety study, known as Study 17P-FU.

Instruments and Procedures

Assessment of the children's longer-term outcomes was performed using the following instruments and procedures:

- The primary endpoint was determined based upon the Ages and Stages Questionnaire (ASQ), completed by the parent or guardian
- Secondary endpoints were based upon items evaluated through use of
    - A Survey Questionnaire, administered by study personnel to the parent
    - Physical examination by a study pediatrician

The ASQ is composed of 19 questionnaires, each corresponding to a specific age window between 4 months and 5 years, and each containing 30 developmental items addressing five areas: communication, gross motor, fine motor, problem solving, and personal-social. The instrument was developed on a population including both children considered to be at risk for developmental problems and a normative sample of full term children with no health or developmental concerns. It has been validated against common professional assessment scales, including the Bayley Scales of Infant Development and the McCarthy Scales of Children's Abilities. The questionnaires are designed to identify young children who are in need of further evaluation and early intervention services. Cutoff points, generally corresponding to scores falling 2 standard deviations (SD) below the mean for the combined "at risk" and normal population, were generated for each of the five developmental domains assessed.

The Survey Questionnaire used in this study was derived from questions that were developed and reportedly validated by the following sources: the 2001 Child Health Supplement of the National Health Interview Survey, the 1991 National Maternal and Infant Health Survey, Early Childhood Longitudinal Survey (Department of Education), and the Avon Longitudinal Study of Parents and Children. This questionnaire was not formatted for self-administration; therefore it was administered by study personnel during the clinic visit. The Survey Questionnaire included evaluation of:

- Overall activity level and motor control, compared to age mates of the child, as measured by questions from the Early Childhood Longitudinal Study, Kindergarten (ECLSK), answered by the parent. If a perceived problem was reported by the parent, further questioning determined whether a professional evaluation and diagnosis had been made.
- Vision or hearing problems, assessed by questions from the National Health Interview Survey (NHIS), answered by the parent.
- Assessment of height, weight and head circumference, compared to reference curves generated by the Centers for Disease Control (CDC).
- Gender-specific behavior, assessed by the Pre-School Activities Inventory (PSAI).
- Diagnosis by a healthcare provider of cerebral palsy, asthma, allergic disorders, sensory disorders and neurodevelopmental disorders including attention deficit hyperactivity disorder (ADHD).

Medical Reviewer's Comment

- *Although the ECLSK was developed for use with children from kindergarten to fifth grade, the motor control and activity questions were reviewed by an NICHD developmental psychologist, who reportedly determined that they were appropriate for children as young as two. The basis for this conclusion was not provided.*

A general physical examination was conducted by a pediatrician or nurse practitioner at the study center, and included measurements of the child's current weight, height, head circumference, and blood pressure, as well as the documentation of any major abnormality. In addition, a part of the examination was specifically directed toward the identification of genital abnormalities. If the child had a physical examination within the last year, and the parent/guardian was unable to bring the child in for a visit, the information from that previous physical examination was entered into the study database. In these cases, the medical record of the child was abstracted by an NICHD pediatrician.

Following IRB approval, MFMU Network study personnel attempted to locate the women who participated in Study 17P-CT-002. If the mother who was enrolled in Study 17P-CT-002 could not be found, but her child could be located, the child's father or guardian could enroll the child in this study.

The nurse used a standardized script to request consent to participate. If the parent was willing to allow the child to participate, the nurse obtained informed consent by mail. She also made arrangements for the child to visit the Network center accompanied by the parent. In addition, the ASQ was mailed to the parent with instructions to bring the completed form to the visit. If the parent was unable to attend a follow-up visit, the research nurse administered the Survey Questionnaire by telephone, and asked the parent to mail back the completed ASQ.

The following procedures were conducted at the study visit:

- Administration of the Survey Questionnaire
- Physical examination
- Completion of the ASQ, if not done prior to the study visit

Parents were instructed to complete the ASQ based on the age of the child at the follow-up visit. The ASQ recommends using gestational age-corrected age only until 24 months and since all children to be evaluated were at least two years of age, corrected age was not used in this study. The completed ASQ was scored by the Biostatistical Coordinating Center (BCC) and results were sent back to the study nurse. If a child fell below a pre-established cutoff (below 2 SD from the mean) in at least one of the five developmental domains on the ASQ, the study nurse was to inform the parent/guardian that the child might need additional evaluation in the particular developmental area.

At the time of enrollment in Study 17P-FU, some of the mothers had already been informed of their treatment assignment in Study 17P-CT-002. If they had not been informed, the treatment group was not revealed before the follow-up assessments. Less than 10% of the mothers were informed of their treatment (8.3% in the 17OHP-C group and 7.1% in the placebo group). The

physicians or nurse-practitioners who performed the physical examinations were blinded to the treatment group assignment of the mother.

Inclusion/Exclusion Criteria

Inclusion Criteria

1. Maternal enrollment in the Study 17P-CT-002 conducted at one of the 14 Network centers in the fourth MFMU Network cycle (2001-present). As the composition of the MFMU changes over time, only women initially enrolled at a site that remained in the Network were eligible for the follow-up study.
2. Infant discharged alive from birth hospitalization.

Exclusion Criteria

No exclusion criteria were defined in the protocol.

Primary and Secondary Endpoints

The primary objective of the study was to determine if there were differences in achievement of developmental milestones between children whose mothers received 17OHP-C and those who received vehicle in Study 17P-CT-002, as measured by the ASQ. The primary endpoint was the proportion of children from each treatment arm who fell below a specified cut-off on at least one of the five developmental areas measured on the ASQ.

The secondary objectives of the study were to determine if differences existed between children whose mothers received 17OHP-C and those who received vehicle in Study 17P-CT-002 in the following factors:

- Gender-specific play
- Physical growth (height and weight)
- Activity levels
- Motor control
- Vision or hearing difficulties
- Physician- or other health provider-diagnosed conditions, such as asthma, allergic disorders, sensory disorders, and neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD), as reported on the Survey Questionnaire

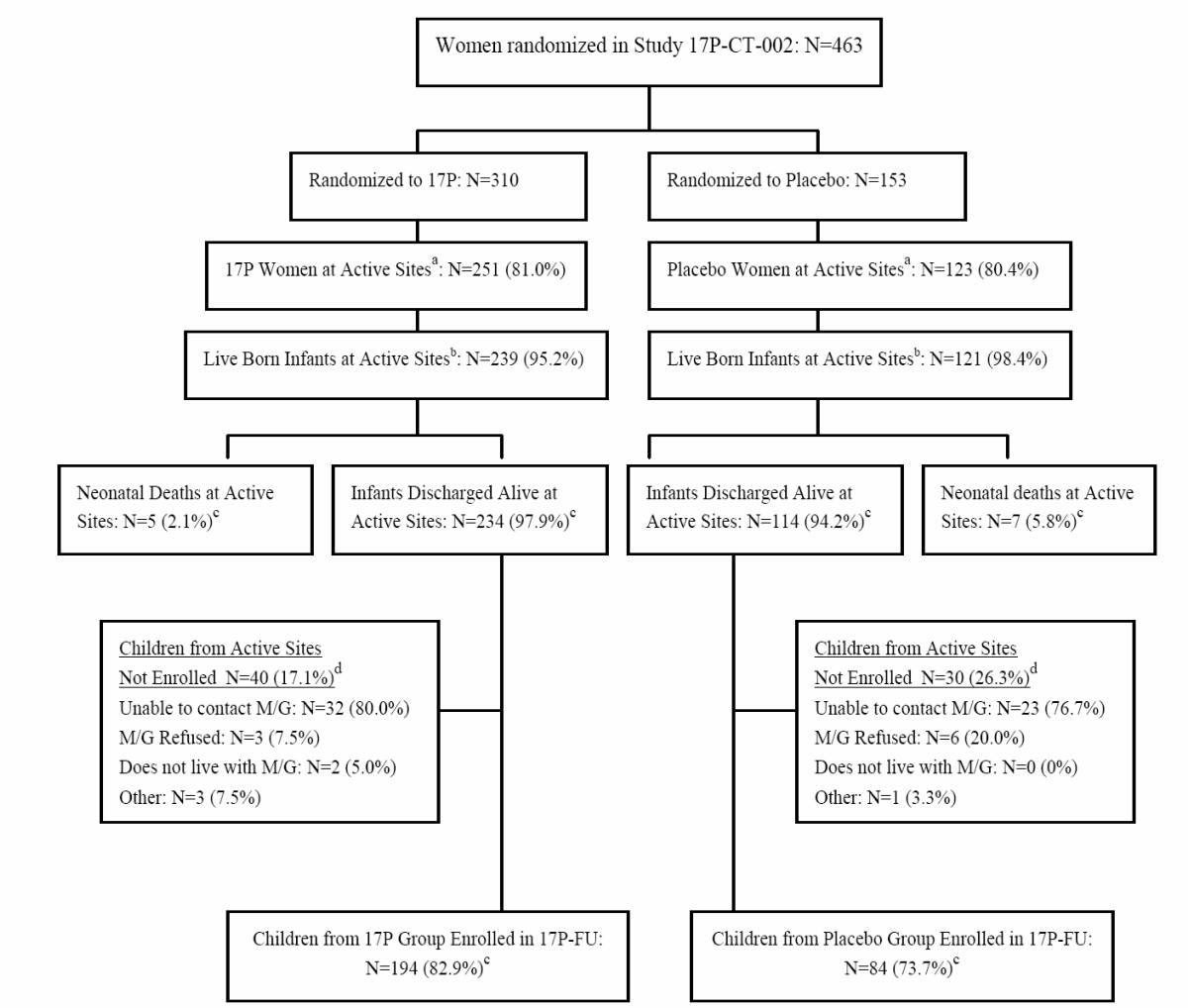
Subject Disposition

Figure 3 shows the disposition of infants born alive to mothers in Study 17P-CT-002. A total of 463 women were randomized to study drug; 310 women received 17OHP-C and 153 women received vehicle. Of those women, a total of 374 women (251 [81.0%] of the 17OHP-C women and 123 [80.4%] of the vehicle women) were enrolled at one of the 14 study sites still active in the MFMU Network at the start of this follow-up study. These women had a total of 360 live born infants, representing 74% of the 446 live births in Study 17P-CT-002. Twelve infants from the active sites died before discharge from the birth hospitalization, five (2.1%) of the 239 in the 17OHP-C group and seven (5.8%) of the 121 in the vehicle group. There were no deaths

following discharge from the nursery in children from the subset of mothers who were able to be located.

Of 348 eligible children, 278 (79.9%) were enrolled in Study 17P-FU. The percentage of eligible children who were enrolled in Study 17P-FU was greater in the 17OHP-C group (82.9% of the 17OHP-C-exposed vs. 73.7% of vehicle-exposed). Inability to contact the parent was the primary reason children were not enrolled. A greater proportion of vehicle-treated mothers refused to allow their child to participate (5% of eligible vehicle mothers vs. 1% of 17OHP-C-treated mothers)

Figure 3 Disposition of Subjects in Follow Up Study 17P-FU



Abbreviations: M/G = mother/guardian
[a] An active study site was a clinical center participating in the MFMU Network at the time Study 17P-FU was conducted.
[b] Percentages were based on the number of patients from active study sites.
[c] Percentages were based on the number of live born infants in Study 17P-CT-002 from active study sites.
[d] Percentages were based on the number of live born infants in Study 17P-CT-002 discharged from birth hospitalization from active study sites.

Source: Section 10.1, Figure 10-1, Final Report for Study 17P-FU.

Demographics and Other Baseline Characteristics

Demographics

The children ranged in age from 30 to 64 months at the time of enrollment. The mean age was similar for the 2 treatment groups (47.2 months for 17OHP-C vs. 48.0 months for the vehicle group), as was the distribution across the race/ethnic groups, which was assigned based on the mother's race or ethnicity. The majority of children were of African American descent (54.1% in the 17OHP-C group and 56.0% in the vehicle group), with children of Hispanic descent comprising 14.9% (17OHP-C) to 17.9% (vehicle). Approximately one-fourth of the children were Caucasian. The 17OHP-C group had 58.3% male children compared with 47.6% in the vehicle group.

Neonatal Outcomes of Enrolled Children

The neonatal outcomes of the enrolled children are listed in Table 23
The gestational age at delivery ranged from 25.0 to 41.9 weeks, with a mean gestational age of 37.3 weeks in the 17OHP-C group and 36.2 weeks in the vehicle group. This was slightly greater than the mean gestational ages observed in the total population in Study 17P-CT-002 (36.2 weeks for 17OHP-C vs. 35.2 for vehicle).

Birthweight ranged from 714 - 4900 g in the 17OHP-C group and 615 - 4855 g in the vehicle group. The 17OHP-C group had a lower percentage of infants with birthweight <2500 g (21.8% vs. 34.5%) and <1500 g (4.7% vs. 8.3%). The mean and range of APGAR scores were comparable between the 2 treatment groups.

Table 23 Neonatal Outcomes of Enrolled Children

Characteristic	17OHP-C	Vehicle
Gestational age at delivery (wks)	N=194	N=84
Mean (SD)	37.3 (3.2)	36.2 (3.7)
Min, Max	25.0, 41.7	25.1, 41.9
Birthweight (g)	N=193	N=84
Mean (SD)	2,914 (707.8)	2,756.7 (813.7)
Min, Max	714, 4900	615, 4855
Birthweight <2500 g, n (%)	42 (21.8)	29 (34.5)
Birthweight <1500 g, n (%)	9 (4.7)	7 (8.3)
Head Circumference (cm)	N=188	N=82
Mean (SD)	32.8 (2.5)	32.2 (3.2)
Min, Max	23.0, 37.5	21.5, 38.0
1 Minute APGAR	N=191	N=84
Mean (SD)	7.8 (1.6)	7.6 (1.7)
Min, Max	1.0, 9.0	1.0, 9.0
APGAR <3, n (%)	5 (2.6%)	3 (3.6)
5 Minute APGAR	N=192	N=84
Mean (SD)	8.7 (0.8)	8.7 (0.9)
Min, Max	3.0, 10.0	3.0, 9.0
APGAR <3, n (%)	0	0

Source: Table 11-2 Final Report for Study 17P-FU.

The incidence of preterm births in the follow-up population is summarized in Table 24. At each of gestational ages <37, <35, and <32 weeks, the percentage of infants in the 17OHP-C treatment groups was numerically lower than that in the vehicle group.

Table 24 Pregnancy Outcomes in the follow up Population

Pregnancy Outcome (Weeks Gestation)	17OHP-C N=194	Vehicle N=84
Delivery <37	30.4%	52.4%
Delivery <35	14.9%	25.0%
Delivery <32	7.2%	13.1%

Source: Table 11-2 Final Report for Study 17P-FU.

Medical Reviewer's Comment

- *The 17OHP-C and vehicle treated children in the follow-up study may represent a slightly lower risk subset of the total population of study 17P-CT-002, as their mean gestational ages*

were one week greater than the total population of 17OHP-C and vehicle treated children. The 17OHP-C treated children also had attained greater gestational age and birthweight than their vehicle-exposed peers in the follow-up study. However, this latter finding is reflective of the outcome of the primary study 17P-002-CT, namely, children from mothers treated with 17OHP-C were on the average one week older at birth.

Neonatal Morbidity of Enrolled Children

The neonatal morbidities reported at birth for the children enrolled in this study are summarized in Table 25. All occurred with equal or greater frequency in the vehicle group as compared to the 17OHP-C group. The differences between the 17OHP-C and vehicle groups in the follow-up study were not analyzed statistically. The largest between-group differences (≥4 percentage points) were observed in the incidence of any IVH (1.6% vs. 6.0%) and use of supplemental oxygen (15.5% vs. 21.4%), which were neonatal morbidities that were also lower in the 17OHP-C group in the total population in Study 17P-CT-002.

Table 25 Percentage of Enrolled Neonates Experiencing Morbidities

Morbidity	17OHP-C N=193 (%)	Vehicle N=84 (%)
Transient tachypnea	5.2	8.3
Respiratory distress syndrome	9.3	10.7
Bronchopulmonary dysplasia	1.6	3.6
Persistent pulmonary hypertension	0	0
Ventilator support	8.3	10.7
Supplemental oxygen	15.5	21.4
Patent ductus arteriosus	3.1	3.6
Seizures	0	0
Any intraventricular hemorrhage (IVH)	1.6	6.0
Grade 3 or 4 IVH	0.5	0
Other intracranial hemorrhage	0	1.2
Retinopathy of prematurity	2.1	3.6
Proven newborn sepsis	2.1	2.4
Confirmed pneumonia	1.0	2.4
Necrotizing enterocolitis	0	1.2

Source: Table 11-3, Final Report for Study 17P-FU.

The mean and median duration of respiratory therapy for the infants enrolled in the follow-up study were 1.5 and 0.0 days (range: 0.0, 74.0 days) for infants in the 17OHP-C group and 1.9 and 0.0 days (range: 0.0, 44.0 days) for infants in the vehicle group.

Safety Outcomes

Safety assessments were collected via the ASQ, the Survey Questionnaire, and the physical examination. On the Survey Questionnaire, the parent was asked to report any medical diagnosis or operations that occurred between discharge from the birth hospitalization and the time the questionnaire was completed. During the physical examination, the physician was to document any medical abnormality.

Missing data on the ASQ were imputed with the mean of the scores for other items in the same developmental area, as long as ≤ 2 items were missing. If > 2 items were missing, that developmental area was considered missing, and the primary outcome was determined based on the remaining areas. On the PSAI, missing items were imputed with the mean score for that item from the entire sample of same-gender children. If >2 items were missing, the questionnaire was not used. No imputation of missing data was done for other items.

Primary Outcome: Findings from Age and Stages Questionnaire (ASQ)

The ASQ was completed for 275 children, 193 from the 17OHP-C group and 82 from the vehicle group. The age of the children at the time of completion of the ASQ ranged from 30 to 64 months; mean age at time of completion did not differ between the 17OHP-C and vehicle groups (47.2 vs. 48.0 months). (See Table 26)

Table 26 ASQ – Age of Child at Completion, Source of Information, and Where Completed

	17OHP-C N=193[A] n (%)	Vehicle N=82[A] n (%)
Age ASQ Completed (months)		
30	1 (0.5)	0
33	9 (4.7)	3 (3.7)
36	30 (15.5)	8 (9.8)
42	49 (25.4)	25 (30.5)
48	32 (16.6)	12 (14.6)
54	38 (19.7)	17 (20.7)
60	34 (17.6)	17 (20.7)
Mean (SD)	47.2 (8.6)	48.0 (8.4)
Median	47.1	48.2
Min, Max	30.2, 63.9	33.5, 64.3
Who Completed Majority of ASQ		
Mother	114 (59.1)	53 (64.6)
Father	2 (1.0)	4 (4.9)
Grandparent	2 (1.0)	0
Foster Parent	1 (0.5)	0
Guardian	2 (1.0)	0
Study Nurse	72 (37.3)	25 (30.5)
Where ASQ Completed		
Home	84 (43.5)	40 (48.8)
Clinical Center	94 (48.7)	34 (41.5)
Home and Clinical Center	15 (7.8)	8 (9.8)

[A] Number of children with ASQ data.
Source: Section 12.3.1, Table 12-1 Final Study 17P-FU-Report

Medical Reviewer's Comment

- *At the time that the ASQ was completed, the children in 17OHP-C group tended to be slightly younger, with 21% ≤ 3 years of age, as compared to 14% of vehicle children. However, this did not have an impact on the percent of children who scored below cut-off (see Table 26).*

The ASQ was completed predominately by the mother (59.1% 17OHP-C vs. 64.6% vehicle) or the study nurse (37.3% vs. 30.5%), and was equally likely to be completed in the home as in the clinical center.

The ASQ responses were categorized to assess communication, gross motor, fine motor, problem solving, and personal-social. Using threshold scores (cutoffs) for normal development, the percentages of children who had scores below the cutoffs for the five areas of development were determined.

Table 27 shows the percentage of children in each treatment group whose ASQ scores suggested developmental problems in at least one of each of the five areas. As the cutoff for identifying a child as needing further developmental evaluation is based, according to the Applicant, on the mean for a normal population, the ASQ would be expected to identify about 20% of "at risk" children evaluated as possibly delayed. The percentage of children who scored below the cutoff in at least one developmental domain was comparable (27.5% in the 17OHP-C group and 28.0% in the vehicle group [p=0.9206]).

The proportion of children below the cutoff in each developmental domain was similar for each treatment group. The area with the highest percentage of children with low scores was fine motor skills, with approximately one in five children scoring below the cutoff (20.7% in the 17OHP-C group vs. 18.3% in the vehicle l group). Approximately one in ten children had scores below the cutoff in communication and/or problem solving. Few children had low scores for gross motor and personal-social skills.

Table 27 Percentages of Children in Each Treatment Group Whose ASQ Scores Suggested Developmental Problems

	17OHP-C N=193		Vehicle N=82	
	n	%	n	%
Occurrence of score <cutoff on at least one developmental area	53	27.5	23	28.0
Area of Development				
Communication	22	11.4	9	11.0
Gross Motor	5	2.6	3	3.7
Fine Motor	40	20.7	15	18.3
Problem Solving	20	10.4	9	11.0
Personal-Social	7	3.6	1	1.2

Source: Table 12-2, Final Report for Study 17P-FU.

Medical Reviewer's Comment

- *The vehicle-exposed children had a greater frequency of very low birthweight (<1500 gm) and delivery prior to 32 weeks (see Table 23 and Table 24). It would be expected that a higher proportion of vehicle treated children would be at risk for developmental delays on the basis of these perinatal risk factors. The classification of equal proportions (about 28%) of children in each group as possibly delayed suggests that the 17OHP-C group also resembled an "at risk" group, albeit not as strongly attributable to low birthweight and gestational age. The Applicant did not conduct an analysis adjusting for these risk factors in assessing the proportion of possibly delayed children in each treatment group.*

Secondary Outcomes from Survey Questionnaire

A similar proportion of the children in the 17OHP-C group (99%) and the vehicle group (98%) had a completed Survey Questionnaire. Results of the various developmental areas assessed as secondary endpoints are shown in Table 28. There were no marked differences between the groups. A slightly higher proportion of the vehicle group had diagnosed problems with motor skills, activity level, communication problems, inability to pay attention/learn, hearing, or ability to walk/run/play. The most common reported diagnoses were inability to pay attention/learn, hearing impairment, and impairment in ability to walk/run/play. When the category inability to pay attention/learn is broken down further (not shown in Table 28) the most frequent causes included "developmental delay," (reported for 2.6% of the 17OHP-C children and 3.7% of the vehicle children), and ADHD/ADD, (0.5% in the 17OHP-C group and 2.4% in the vehicle group). A child in the 17OHP-C group had a reported diagnosis of mental retardation (Down syndrome) and another child in the 17OHP-C group had a reported diagnosis of autism.

Sensory impairments and need for special equipment were uncommon, but minimally more frequent in vehicle-treated children. More than 90% of the children in both treatment groups were reported to have height and weight within the normal range, according to CDC reference growth curves. Almost all of the children in both treatment groups were either in excellent, very good, or good health (98% vs. 95%). No differences in gender-specific roles were noted.

Table 28 Developmental Assessment Based on the Survey Questionnaire

Developmental Area (Scale included in Questionnaire)	Evaluation	17OHP-C N=193		Vehicle N=82	
		n	%	n	%
Motor Skills (ECLSK)	% with diagnosis	1[A]	0.5	1[B]	1.2
Activity Level (ECLSK)	% with diagnosis	2	1.0	1	1.2
Communication problems	% with diagnosis	9	4.7	7	8.5
Inability to pay attention/learn	% with diagnosis	8	4.2	5	6.1
Hearing Impairment (NHIS)	% with problem	4	2.1	5	6.1
Vision impairment (NHIS)	% with problem	4	2.1	2	2.4
Need for special equipment	% with problem	1	0.5	1[b]	1.2
Impairment in ability to walk/run/play	% with problem	5	2.6	5	6.1
Overall health	% with "fair health"	4	2.1	4	4.9
	% with "poor health"	0		0	
Height	% below normal	7	3.8	4	5.2
Weight	% below normal	11	5.8	6	7.5
		Mean		Mean	
Gender specific roles (PSAI)	Male score	66.5		67.3	
	Female score	31.8		33.1	

[A] Upper body weakness
[B] Cerebral palsy
Source: Tables 12-5, 12-6, 12-7, 12-8, Final report for Study 17P-FU.

Reported Diagnoses by Health Professionals

Parents/guardians were asked to report for the child any diagnoses made by a health professional at any time between discharge from birth hospitalization and enrollment in the follow-up study. The reported diagnoses are summarized in Table 29. The incidence of each type of reported diagnosis was not meaningfully different (i.e., not > 4 percentage points) between the 2 treatment groups.

Table 29 Reported Diagnoses by Health Professionals

Reported Diagnosis	17OHP-C N=192[A] n (%)	Vehicle N=82[A] n (%)
Asthma	39 (20.3)	20 (24.4)
Asthma attack in past 12 months	20 (10.4)	8 (9.8)
Visit to ER or Urgent Care due to asthma in past 12 months	18 (9.4)	7 (8.5)
Eczema or skin allergy	35 (18.2)	12 (14.6)
Ear infections (3 or more)	20 (10.4)	7 (8.5)
Hay fever	19 (9.9)	5 (6.1)
Respiratory allergy	16 (8.3)	9 (11.0)
Developmental delay [B]	14 (7.3)	7 (8.5)
Stuttering or stammering [C]	11 (6.4)	5 (6.6)
Frequent repeated diarrhea or colitis	5 (2.6)	1 (1.2)
Anemia	5 (2.6)	4 (4.9)
Food or digestive allergy	3 (1.6)	3 (3.7)
Seizures or convulsions with fever	3 (1.6)	1 (1.2)
Frequent or severe headaches or migraines [C]	1 (0.6)	2 (2.6)
Diabetes	1 (0.5)	0
Arthritis	1 (0.5)	0
Seizures or convulsions without fever	0	1 (1.2)
Cerebral palsy	0	1 (1.2)
Sickle cell	0	1 (1.2)
Cystic fibrosis	0	0

[A] The number of children for whom the Survey Questionnaire was completed; two children in each treatment group did not have a completed Survey Questionnaire.

[B] Parent/guardian answered "yes" to the question "Has a doctor or other health professional EVER told you that (the child) had any developmental delay?" Per help text provided with the Survey Questionnaire, the parent/guardian was to say "yes" if the health professional diagnosed the child as falling significantly behind age mates in physical, mental, social/emotional, or speech development.

[C] Question answered only for children 3 years or older. Percentages were based on N=171 in 17OHP-C group and N=76 in placebo group.

Source: Table 12-10, Final Report for Study 17P-FU.

Medical Events of Interest

Medical events of interest were potential adverse events that might be attributable to the study drug or to sequelae of prematurity and low birthweight. They were evaluated by integrating data

obtained on the ASQ, from the parent on the Survey Questionnaire, and from study pediatricians who performed physical exams on the children.

Genital and Reproductive Anomalies
As the study drug involved fetal exposure to a progestin, the occurrence of genital and reproductive anomalies was of particular interest. These were identified by parental reports on the Survey Questionnaire and by physician findings on the physical examination.

Six (3.2%) children in the 17OHP-C group and one (1.2%) child in the vehicle group were initially reported by either parent or physician as having genital or reproductive abnormalities. After review of all available data, two findings in the 17OHP-C group were determined to be misclassified, resulting in genital or reproductive abnormalities in 2.1% (n=4) of the children in the 17OHP-C group and 1.2% (n=1) in the vehicle group. The four abnormalities in the 17OHP-C group included:

- micropenis and small scrotal sac noted on study physical examination of a child exposed to 17OHP-C from 19-38 weeks of gestation.
- microphallus and Down Syndrome noted on study physical examination of a child exposed from 18-34 weeks of gestation.
- surgical correction of undescended testes at an unspecified age in a child exposed from 19-41 weeks of gestation.
- early puberty, described by the mother as the cause of joint pain that limited the child's ability to walk/run/play, and noted on physical examination (including 4-5 cm breast buds) in a girl exposed from 20-40 weeks of gestation; she was also at the 100th centile for body mass index.

The single genital/reproductive anomaly in the placebo group was described as "sparse public hair" in a 42 month old girl.

Developmental Delays
A second integrated evaluation concerned identification of the "true positives" among those children tagged as potentially at risk for developmental delay based on their ASQ scores. As the purpose of the ASQ is to identify children who may require further evaluation, only some will have confirmation of a developmental delay upon evaluation by a professional. Those children with at least one below-cutoff ASQ score and who also had a parental report of a diagnosis of developmental delay made independently by a professional were reviewed in more detail.

Thirteen (6.7%) of the 193 children in the 17OHP-C group and 8 (9.8%) of the 82 children in the placebo group had an ASQ score below cutoff for at least one developmental area and a reported diagnosis of developmental delay (either in a specific area or overall). The percentages of children evaluated on the ASQ who scored below the cutoff in a specific ASQ developmental area and had at least one reported diagnosis of developmental delay were as follows:

	17OHP-C n = 13	Vehicle n = 8
Communication:	4.7%	8.5%
Gross motor:	1.6%	2.4%
Fine motor:	5.2%	3.6%
Problem solving:	2.6%	6.1%
Personal-social:	2.6%	1.2%

Of the 21 children meeting both criteria, the most common ASQ domains falling below the cutoff were fine-motor and communication for the 17OHP-C group and communication and problem-solving for the vehicle children.

Developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age mates in physical, mental, social/emotional, or speech development, was reported for a similar percentage of children in the 17OHP-C and vehicle groups (7.3% vs. 8.5%).

Physical Examination

Physical exams were performed by study physicians on 93% of children in the 17OHP-C group and 87% of the vehicle children. Physical examination findings were abstracted from medical records of recent exams for 4% of the 17OHP-C group and 10% of the vehicle children; in the remaining cases, no physical findings were available.

Physical findings occurring with disparate distribution over the 2 groups included heart murmurs and irregular rhythm (in ten 17OHP-C and no vehicle children), and palpable kidneys (in four 17OHP-C and no vehicle children).

Medical Reviewer's Comment

- *The findings of 10 heart murmurs/irregular rhythm in the 17OHP-C exposed children vs. none in the vehicle exposed children warrants further investigation as part of an additional safety study. An increase in cardiac anomalies from 17OHP-C is very unlikely since the anatomic development of the heart is complete at 4-5 menstrual weeks gestation. Some of the mothers were aware of the study arm they were assigned to which could have a bias if she informed the examining pediatrician.*

Summary (FDA Medical Reviewer)

Study 17P-FU assessed the health status of the children born to women who received weekly intramuscular injections of study drug (17OHP-C or vehicle) during Study 17P-CT-002. Only study centers still active in the MFMU Network at the start of Study 17P-FU in the fall of 2004 could participate. Of the 348 infants who were discharged from birth hospitalization at active

study sites, 83% (194/234) of the eligible infants in the 17OHP-C group and 74% (84/114) in the vehicle group were enrolled in Study 17P-FU. As noted previously, both the 17OHP-C and vehicle treated children in the follow-up study may represent a slightly lower risk subset of the total population children of mothers who participated in study 17P-CT-002, given their greater mean gestational age as compared to the total cohort of children from study 7P-CT-002. However, the greater gestational age and birthweight in the 17OHP-C group as compared to their vehicle - exposed peers in the follow-up study reflects the outcome of the primary treatment study (study 17P-CT-002).

There was no difference between the 17OHP-C and vehicle groups in the percentage of children who scored below the cutoff for at least one developmental area of the ASQ. The percentages of children who scored below the ASQ cutoff in each of the individual five developmental areas were similar in the 17OHP-C and vehicle groups.

Developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age mates in physical, mental, social/emotional, or speech development, was reported for a comparable percentage of children in the 17OHP-C and vehicle groups.

Review of Study 17P-FU by Non-FDA Consultant

The division requested that (b) (4) review and provide comments for Study 17P-FU. A summary of her review follows:

"This study provided follow-up data on safety and efficacy of 17P treatment for babies through at least age 2 yrs whose mothers were enrolled in the trial, a safety assessment of developmental milestones and physical health of exposed children was conducted in 14 of the original 19 enrollment sites. There were 429 live births from all sites. Ninety-eight from the 5 non-participating sites were not included in the follow-up. Two hundred seventy-eight babies (65% subjects' live offspring) participated in the follow-up study. This included 68% of babies exposed to 17P and 59% of babies exposed to placebo. The primary objective of the study was to determine if there were differences in achievement of developmental milestones between children whose mothers received 17P and those who received Placebo in Study 17P-CT-002, as measured by the Ages and Stages Questionnaire (ASQ). Secondary outcomes included differences in gender-specific play, physical growth (height and weight), activity levels, motor control, vision or hearing difficulties, physician- or other health provider-diagnosed condition. The assessments included the ASQ, a Survey Questionnaire, and a physical exam performed by a physician or nurse practitioner. The ages of the children at follow-up were mean ~48 months in both groups. The sample size had only a 50-60% power to detect an absolute difference of 10% and >80% power to detect a 15% absolute difference."

Major findings

"There were no deaths in either group after hospital discharge.

There were no differences between the groups for developmental delays determined by the ASQ. The occurrence of a score below the cutoff on at least one area of development was 27.5% in 17P group and 28% in placebo group. There were also no differences in the survey questionnaire. Growth was similar in the groups and medical conditions reported by health professionals were similar. Only one child was diagnosed with cerebral palsy in the placebo group."

Critique

Strengths

"The use of the ASQ as instrument to screen subjects in the age range of the subjects was appropriate for developmental delays. This instrument is an excellent screening tool with good validity. When compared to standard psychometric assessments, it has a high negative predictive value, so that those children who pass are likely normal. The investigators were able to obtain follow-up data on 80% of available subjects despite there had not been an initial intent to follow these children. The data collection, verification, etc. appears to have been of high quality."

Weaknesses

"Due to the change in centers in the MFMU Network, children from 5 centers were not assessed. Therefore only 65% of live born children exposed to study drug or placebo in utero were evaluated for this follow-up assessment. Although it was stated in the protocol (p.147 of 237) that a sensitivity analysis to include non-responders or those lost to follow-up with different assumptions regarding their outcomes would be performed to determine whether the results are robust, this analysis is not included in the report. This might be helpful in the evaluation of the reported results."

"The contribution of center to the outcomes was not analyzed. One center, U. Alabama at Birmingham contributed 30% of the placebo and 35% of 17P subjects with much smaller contributions from the other 13 sites."

"The major weakness of the study is that the data was primarily dependent on parental report. Although the ASQ is an excellent screening tool, it is meant to be combined with other strategies as part of a comprehensive follow-up of at-risk infants. For the infants who received a score >2 SD below the mean on the ASQ, the parents were to be notified that their child may need additional evaluation of their development. Was this done and did the study investigators follow-up on the testing results? In an evaluation of the ASQ, Skellen (2001) found that the ASQ agreed with standard pyschometric tests 67% when assessing 14 children with known disabilities. It would have strengthened this study if those children who failed the screening ASQ were then formally evaluated by an age-appropriate standard pyschometric test."

"The rate of ASQ score below the cutoff was higher in both groups (28%) than expected (2.5 to 12%). Although this was attributed to the high rate of preterm births <37 wks, there were few children who were <32 wk in the study (N=25) and of those summarized who had score below the cutoff on ASQ and a diagnosis of developmental delay, 10 of 21 were $>36^0$ wks gestation. It would have been helpful to have included a comparison group of term infants matched for ethnic and socioeconomic characteristics as the study infants."

"The Survey Questionnaire relied on parent report of a health provider telling them of certain diagnoses including developmental delay. It is possible that even if a pediatrician had noted a delay, he/she may not have used that terminology or sufficiently explained it to a parent."

"There is no evidence that a neurologic exam was performed as part of the assessments. The physical exam form does not include assessment of muscle tone, deep tendon reflexes, dexterity, gait, or balance. This is unfortunate, since there was the opportunity to perform these assessments. Only one child had a diagnosis of cerebral palsy by report."

"Although the objective of the follow-up study was to assess long term safety of 17P and not efficacy, it would be reasonable to expect that a lower rate of preterm birth would improve neurodevelopmental outcome compared to placebo. The original sample size was not powered to address this outcome, but interventions to prevent preterm births that do not impact on the long term outcomes of children born to mothers at risk will not affect the major cost of preterm birth (i.e. life long disabilities, medical morbidities)."

Recommendations of (b) (4)

- If additional safety and efficacy trials of 17P are recommended, long-term assessment at age 18 to 24 months of the children should be included in the study design. The age range 18 to 24 months as an assessment age is proposed to balance the challenge of the potential for loss to follow-up in longitudinal studies and an adequate time to identify major neurodevelopmental problems. At age 18 to 24 months, most cases of cerebral palsy and mental retardation can be identified by appropriate assessments. In addition for studies of drug exposure in preterm infants, there are many publications of neurodevelopmental outcomes of children in this age range.

- A strategy to include formal psychometric assessment for subjects who fail the screening assessment should be included in future study design. Appropriate tests would include the Bayley Scales of Infant Development III (BSID-III) for children 1-42 months, the McCarthy Scales of Children's Abilities for ages 2.5 to 8.5 years, the Wechsler Pre-school and Primary Scale of Intelligence (WPPSI) for ages 3-7 yrs, and the Wechsler Intelligence Scale for Children (WISC) for ages 7-16 (to name a few). A careful assessment of neurologic status preferably by a neurologist or developmental pediatrician should be included in future studies.

Medical Reviewer's Comments

- *This follow-up study of 278 children up to 64 months of age showed an ASQ score below the cutoff that was higher in both groups (28%) than expected (2.5 to 12%). Although this was attributed to the high rate of preterm births <37 wks, 10 of 21 children were >36^0 weeks gestation at birth, indicating other risk factors in this population.*
- *There was no difference between the 17OHP-C and vehicle groups in the percentage of children who scored below the cutoff for at least one developmental area of the primary*

endpoint, the ASQ. The percentages of children who scored below the ASQ cutoff in each of the individual 5 developmental areas were similar in the 17OHP-C and vehicle groups.

- *Developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age mates in physical, mental, social/emotional, or speech development, was reported for a comparable percentage of children in the 17OHP-C and vehicle groups.*
- *Strengths of the study include the use of the ASQ as instrument which is an excellent screening tool with good validity. When compared to standard psychometric assessments, it has a high negative predictive value. The investigators were able to obtain follow-up data on 80% of available subjects despite there not being an initial intent to follow these children post discharge after birth.*
- *The major weakness of this study is that it was planned and conducted five years after the end of the principal study. By that time, five of the original 19 centers were no longer part of the MFMU Network. As such, the sample size had only a 50-60% power to detect an absolute difference of 10% and >80% power to detect a 15% absolute difference. One center (University of Alabama) contributed more than 30% of the subjects. Another weakness was that the data was primarily dependent on parental report. Ideally the ASQ screen positive children would have been followed up with a neurological exam and a formal psychometric exam (e.g. the Bayley's development scales). .*
- *This reviewer recommends that the applicant conduct another follow-up study as part of another safety study to address the weaknesses in this study.*

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no known abuse potential with this drug

7.1.14 Human Reproduction and Pregnancy Data

All subjects in this study were pregnant. There is one study in the literature that found a decreased sex drive in adolescent males exposed to synthetic progesterone. The exact formulation was not specified. This study was published in Psychoendocrinology; Patricia Kester was the investigator. Fifty eight young adult males exposed to one of four hormone regimens were matched against non-hormone exposed controls. 13 of the subjects were exposed to synthetic progesterone. Subjects were interviewed for various aspects of psychosexual development, and administered the Bern sex-role Inventory (BSRI), the Guilford-Zimmerman Temperament Survey (GZTS), the Strong Vocational Interest Blank (SVIB) and the Embedded Figures Test (EFT). Synthetic progesterone exposed subjects had some sex atypical childhood behaviors (e.g. more females in the peer group), and a lower rating of sex drive along with a later onset of intercourse in adulthood. See section 7.1.4 regarding literature on human reproduction.

Medical Reviewer's Comment

- *This study supports the need for additional long term post-approval data on reproductive health in adolescents.*

7.1.15 Assessment of Effect on Growth

Growth was evaluated in the 17P-FU report. More than 90% of the children in both treatment groups were reported to have height and weight within the normal range, according to CDC reference growth curves.

7.1.16 Overdose Experience

No subjects in the clinical trials were reported to have received an overdose of 17 OHP-C. All injections are given by health care providers so the potential for intentional overdose is minimal.

Medical Reviewer's Comment

- *Several studies have been reported in the literature using doses which were 2 to 3 fold higher than this dose. No untoward effects have been reported.*

7.1.17 Postmarketing Experience

A consult was sent to the Division of Drug Risk Evaluation (DDRE) to assess any adverse events related to compounded preparations of 17 α-hydroxyprogesterone caproate from June 2003 to present. Only four reports were received in AERS since June 2003. Three reports referred to product use up to 17 weeks gestation: (1) a case of an infant born with microcephaly, intrauterine growth restriction, and Epstein's anomaly of the heart (the mother also had a "problem with alcohol"); (2) a case of neonatal cyanosis and congenital heart valve disorder; and (3) a mother with "transient parkinsonism".

Medical Reviewer's Comment

- *In all cases, 17OHP-C was taken prior to 17 weeks gestation.*
- *These case are too few to draw any strong conclusions about the safety of 17OHP-C but do not raise any concerns.*

Because there were so few reports since June 2003, all reports submitted for Delalutin® were also reviewed; the complete list was 154 reports in the AERS database from June 1969. Approximately 30% of these reports involved a congenital anomaly. Approximately 10% involved multiple congenital anomalies.

Medical Reviewer's Comments

- *The preponderance of reported congenital anomalies may be due to 1973 federal register in which there was a warning that Delalutin (and other progestins) may cause congenital anomalies. A subsequent publication of the federal register (1999) refuted these claims, stating that there was no evidence that Delalutin cause congenital anomalies.*
- *Although no definitive conclusions can be made from these reports, the nature and number of reports for a drug that had been marketed for almost 50 years is not worrisome .*

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The Applicant submitted data from two active treatment clinical trials and a follow-up safety study: Study 17P-IF-001; Study 17P-CT-002 and follow up study 17P-FU.

Initial Formulation Study (Study 17P-IF-001)
This study was terminated because the active study drug (17OHP-C) was recalled by its manufacturer, under the direction of the FDA, due to violations of manufacturing practices potentially affecting the potency of the drug. At the time of termination, only 150 of the proposed 500 subjects had been randomized, and no data analysis had been done. Eighty six subjects completed the treatment regimen before the study was stopped: 57 (61%) of the 17OHP-C subjects and 29 (52%) of the placebo subjects. The study drug used in this terminated study is referred to as the Initial Formulation (IF).

Principal Clinical Trial (Study 17P-CT-002)
This study, which began in October 1999, randomized 463 subjects who had at least one documented prior spontaneous preterm birth of a singleton, non-anomalous fetus. Of these, 418 subjects (90.3%) completed dosing through 36^6 weeks or birth: 279 (90.0%) in the 17OHP-C group and 139 (90.8%) in the placebo group. This study was terminated prior to enrolling the proposed 500 subjects because the pre-specified stopping criterion for efficacy was attained at an interim analysis.

Pooling of Data
Since the potency of the recalled drug in the initial study was in question, the data collected from subjects enrolled in that terminated study were analyzed separately in the NDA and the results are also summarized separately.

Follow-up of Children from the 17P-CT-002 trial (Study 17P-FU)
This was a follow-up safety study to Study 17P-CT-002. The children were at least 2 years of age at the time of the follow-up assessments. The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received weekly intramuscular injections of 17OHP-C compared with placebo during the pregnancy in Study 17P-CT-002. Only 14 of the original 19 sites were remaining in the Maternal-Fetal Medicine Network at the time that the follow up study was conducted. Therefore, approximately 80% of the children were eligible to participate. Of these eligible children, 278 enrolled: 194 from the 17OHP-C arm, and 84 from the vehicle arm.

Medical Reviewer's Comments

- *The Advisory committee concluded that the data submitted was adequate to evaluate safety pre-approval; however they recommended that the applicant conduct another study post-*

approval to evaluate the potential safety signal of increased miscarriages in the 17OHP-C arm.

- *This reviewer agrees with this recommendation.*

7.2.1.1 Study type and design/patient enumeration

Table 30 lists all submitted studies with the study type, design, and subject enrollment.

Table 30 Studies of 17OHP-C for Prevention of Recurrent Preterm Births

Protocol # /Status	Study Design	Study Population	Treatment Dose	Duration of Drug Treatment	Number of Subjects Enrolled	Number of Black/Non-Black Subjects	Mean Age (Range)
17P-IF-001 Terminated Mar 1999[A]	Double-blind, Vehicle-controlled, Randomized 2:1 active treatment to Vehicle	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 37^0 wks gestation or delivery	Total: 150 17P: 94 Vehicle: 56	Total: 95/55 17P: 54/40 Vehicle: 41/15	26.2 yr (17, 42)
17P-CT-002 Completed Aug 2002[B]	Double-blind, Vehicle-controlled, Randomized 2:1 active treatment to Vehicle	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation until 37^0 wks gestation or delivery	Total: 463 17P: 310 Vehicle: 153	Total: 273/190 17P: 183/127 Vehicle: 90/63	26.2 yr (16, 43)
17P-FU Completed Nov 2005	Observational long-term safety follow-up for Study 17P-CT-002	Infants discharged live in Study 17P-CT-002	None	No study treatment was administered	Total: 278 17P: 194 Vehicle: 84	Total: 152/126 17P: 105/89 Vehicle: 47/37	47.4 mo (30, 64)

[A] Study 17P-IF-001 was terminated early by the Sponsor when the manufacturer recalled the study drug. The last subject visit was in August 1999. Of the 150 subjects, 104 subjects (65 randomized to 17OHP-C and 39 randomized to vehicle) had ended their treatment prior to the study termination either because they had completed treatment with study drugs completed study treatment to 36^6 weeks of gestation or delivery or had withdrawn prematurely for reasons other than recall of study drugs.

[B] An independent Data and Safety Monitoring Committee (DSMC) reviewed the study data after 400 subjects had completed the study. Based on that interim dataset, the primary endpoint, birth <37 weeks of gestation, was significantly reduced and the p-value was below the p-value specified in predefined stopping rules. The DSMC recommended that enrollment in the study be stopped, so that no new subjects would be assigned placebo. By the time the study was stopped, 463 subjects had been enrolled, which was 92.5% of the proposed sample size of 500 subjects.

Source: Prepared by Medical Reviewer from final Study Reports.

7.2.1.2 Demographics

Study 17P-CT-002

The patients randomized to the 2 treatment groups were comparable in mean age, race or ethnic group, BMI prior to pregnancy, marital status, years of education, and substance use during pregnancy (Table 31). The mean age of the patients was 26.2 years (26.0 vs. 26.5 years) and their mean pre-pregnancy BMI was 26.6 kg/m^2 (26.9 vs. 26.0 kg/m^2). Half of the patients were married or living with a partner (51.3% vs. 46.4%), while 39.5% had never been married (38.4% vs. 41.8%). More than half of the patients were African American (59.0% vs. 58.8%); and 4% had a history of diabetes (4.2% vs. 2.6%). During the study pregnancy but prior to randomization, 22% had smoked (22.6% vs. 19.6%), 8% had consumed alcoholic drinks (8.7% vs. 6.5%), and 3% had used street drugs (3.5% vs. 2.6%).

Table 31 Demographics and Baseline Characteristics – Study 17P-CT-002

Characteristic	17P (N=310)	Vehicle (N=153)	P-value
Age, yr			0.2481[d]
Mean (SD)	26.0 (5.6)	26.5 (5.4)	
Min, Max	16, 43	16, 40	
Race or ethnic group, n (%)[a]			0.8736[b]
African American	183 (59.0)	90 (58.8)	
Caucasian	79 (25.5)	34 (22.2)	
Hispanic	43 (13.9)	26 (17.0)	
Asian	2 (0.6)	1 (0.7)	
Other	3 (1.0)	2 (1.3)	
Marital status, n (%)			0.6076[b]
Married or living with partner	159 (51.3)	71 (46.4)	
Divorced, widowed, or separated	32 (10.3)	18 (11.8)	
Never married	119 (38.4)	64 (41.8)	
Pre-pregnancy BMI (kg/m^2)			0.3310[d]
Mean (SD)	26.9 (7.9)	26.0 (7.0)	
Min, Max	15.2, 72.2	16.1, 50.7	
Years of education			0.2175[d]
Mean (SD)	11.7 (2.3)	11.9 (2.3)	
Min, Max	2, 16	3, 16	
Diabetes, n (%)	13 (4.2)	4 (2.6)	0.3954[b]
Smoked cigarettes during pregnancy, n (%)	70 (22.6)	30 (19.6)	0.4647[b]
Alcoholic drinks during pregnancy, n (%)	27 (8.7)	10 (6.5)	0.4172[b]
Used street drugs during pregnancy, n (%)	11 (3.5)	4 (2.6)	0.7822[c]

Reference: Study 17P-CT-002 report, Table 11-1
[a] Race was self-assigned by the women.
[b] P-value from the chi-square test.
[c] P-value from the Fisher's Exact test.
[d] P-value from the Wilcoxon Rank Sum test.

Study 17P-IF-001

Baseline characteristics of the 94 patients in the 17P group and the 56 patients in the Vehicle group were not significantly different (Table 32). The mean age of the patients was 26.2 years (26.4 vs. 25.9 yr) and their mean pre-pregnancy body mass index (BMI) was 26.8 kg/m^2 (26.7 vs. 26.9 kg/m^2). Half of the patients were married or living with a partner (52.1% vs. 46.4%), while 39.3% had never been married (38.3% vs. 41.1%). More than half of the patients were African American (57.4% vs. 73.2%); 3.3% had a history of diabetes (4.3% vs. 1.8%). During the study pregnancy but prior to randomization, 28.0% of patients had smoked (28.7% vs. 26.8%) and 12.0% had consumed alcoholic drinks (13.8% vs. 8.9%). The use of street drugs was higher in the patients randomized to the 17OHP-C group (6.4% vs. 0.0%).

Table 32 Demographics and Baseline Characteristics – Study 17P-IF-001

Characteristic	17P (N=94)	Vehicle (N=56)	P-value
Age, yr			0.6202[b]
Mean (SD)	26.4 (5.7)	25.9 (5.5)	
Min, Max	17, 42	19, 42	
Race or ethnic group, n (%)[a]			0.1492[c]
African American	54 (57.4)	41 (73.2)	
Caucasian	28 (29.8)	10 (17.9)	
Hispanic	12 (12.8)	5 (8.9)	
Marital status, n (%)			0.7489[c]
Married or living with partner	49 (52.1)	26 (46.4)	
Divorced, widowed, or separated	9 (9.6)	7 (12.5)	
Never married	36 (38.3)	23 (41.1)	
Pre-pregnancy BMI (kg/m^2)[e]			0.7666[b]
Mean (SD)	26.7 (7.2)	26.9 (7.3)	
Min, Max	16.0, 47.6	16.8, 51.6	
Years of education			0.4616[b]
Mean (SD)	11.8 (1.8)	12.1 (1.9)	
Min, Max	7, 16	8, 16	
Diabetes, n (%)	4 (4.3)	1 (1.8)	0.6511[c]
Smoking during pregnancy, n (%)	27 (28.7)	15 (26.8)	0.7982[c]
Alcohol use during pregnancy, n (%)	13 (13.8)	5 (8.9)	0.3716[c]
Substance use during pregnancy, n (%)	6 (6.4)	0	0.0843[d]

Reference: Study 17P-IF-001 report; Table 9-1
[a] Race was self-assigned by the women.
[b] P-value from the Wilcoxon Rank Sum test.
[c] P-value from the chi-square test.
[d] P-value from the Fisher's Exact test.
[e] Pre-pregnancy BMI was recorded for 93 and 54 patients in 17P and Placebo groups.

Study 17P-FU-Report
The children ranged in age from 30 to 64 months at the time of enrollment. The mean age was similar for the 2 treatment groups (47.2 months for 17OHP-C vs. 48.0 months for the vehicle group), as was the distribution across the race/ethnic groups, which was assigned based on the mother's race or ethnicity. The majority of children were of African American descent (54.1% in the 17OHP-C group and 56.0% in the vehicle group), with children of Hispanic descent comprising 14.9% (17OHP-C) to 17.9% (vehicle). Approximately one-fourth of the children were Caucasian. The 17OHP-C group had 58.3% male children compared with 47.6% in the vehicle group.

Medical Reviewer's Comments

- *The most striking demographic variable in both studies is the over-representation of African Americans in the subject sample (almost 60%) relative to the U.S. population as a whole. This was considered appropriate by the applicant because preterm births are about twice as likely to occur in this population compared to most others. However, the number of subjects representing other ethnic groups is relatively small for comparisons.*

7.2.1.3 Extent of exposure (dose/duration)

Study 17P-CT-002

The mean number of injections of study drug per patient was 14.1 injections for 17OHP-C patients (range: 1-21 injections) and 13.7 injections for vehicle patients (range: 2-21 injections). See Table 33

Table 33 Dosing Information Study 17P-CT-002

		17OHP-C	Vehicle	Subjects
# randomized subjects		310	153	463
# of injections	n	310	153	463
	Median	16.0	16.0	16.0
	Mean	14.1	13.7	14.0
	S.D.	5.6	5.0	5.4
	Min, Max	1.0, 21.0	2.0, 21.0	1.0, 21.0
Compliance (%)	n	310	153	463
	Median	100	100	100
	Mean	92.6	94.1	93.1
	S.D.	21.3	16.9	20.0
	Min, Max	7.4, 100	17.2, 100	7.4, 100
Full Compliance	n	310	153	463
	n %	271 (87.4%)	134 (87.6%)	405 (87.5%)

Source Table 6 17P-CT-002 Tables Submission

Study 17P-IF-001

This study exposed 94 pregnant women to 17OHP-C with an average of 11.5 injections (range: 1 to 21) compared with 56 pregnant women who received an average of 9.8 vehicle injections (range: 1 to 20). Forty-six (31%) of the 150 subjects, 29 (31%) in the 17P group and 17 (30%) in the Vehicle group, discontinued study drug early due to study termination. See Table 34.

Table 34 Dosing Information Study 17P-IF-001

		17OHP-C	Vehicle	Subjects
# randomized subjects		94	56	150
# of injections	n	94	56	150
	Median	13.0	9.0	10.0
	Mean	11.5	9.8	10.9
	S.D.	6.0	6.1	6.1
	Min, Max	1.0, 21.0	1.0, 20.0	1.0, 21.0
Compliance (%)	n	94	56	150
	Median	100	94.6	100
	Mean	82.3	72.6	78.7
	S.D.	28.7	33.6	30.9
	Min, Max	7.5, 100	7.2, 100	7.2, 100
Full Compliance	n	94	56	150
	n (%)	62 (66.0%)	28 (50.0%)	90 (60.0%)

Source 17P-IF-001 Tables Submission

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other studies were submitted.

7.2.2.2 Postmarketing experience

See section 7.1.17

7.2.2.3 Literature

Data on second trimester miscarriage rates also are available from 4 studies reported in a meta-analysis of published studies (Keirse, 1990)[28.] This data showed a very weak trend toward an increased risk of miscarriage in the 17OHP-C arms as compared to vehicle (odds ratio of 1.30, with 95% confidence interval of 0.61 – 2.74).

Medical Reviewer's Comment

- *The results of the current clinical trial, along with the meta-analysis, demonstrated a trend toward increased second trimester miscarriage.*

See section 7.1.4 for a literature review of long term follow-up case control studies on adolescents exposed to 17OHP-C and other progestins in-utero.

7.2.3 Adequacy of Overall Clinical Experience

The design of these studies was adequate to answer critical questions. Various demographic subsets of subjects were exposed to this drug. Those with the greatest risk for recurrent preterm birth, i.e., history of a previous preterm birth were the target population. Subjects excluded from these studies do not limit the relevance of the safety assessments. However, it is not appropriate to treat women in other risk categories until studies are done in these women.

There were no dose finding studies and different durations of exposure were not evaluated. Previous studies using higher and more frequent dosing regimens have been published. Other than a possible increase in miscarriages associated with 17OHP-C, no other significant safety issues were raised. For a discussion of potential birth defects see section 7.2.7. Limited long term data of the pre-school aged offspring was provided (see section 7.1.12). See section 7.1.4 for a literature review of long term follow-up case control studies on adolescents exposed to 17OHP-C and other progestins in-utero.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The applicant did not provide any special animal or in vitro testing.

7.2.5 Adequacy of Routine Clinical Testing

All subjects received adequate routine prenatal care during this study. This care consisted of routine monitoring of vital signs, routine and risk targeted laboratory evaluations, and assessment of signs and symptoms.

No samples for laboratory tests were analyzed as part of this study. Clinical situations that warranted the delivery of the subject or any other medical interventions were acted on by the managing clinician.

Medical Reviewer's Comments

- *This reviewer does not think that study related laboratory data will inform the decision whether or not to approve this drug.*
- *The 1979 Delalutin label mentions the following laboratory alterations:*
  - *Inhibition of gonadotropic hormones – not relevant in pregnant patients*
  - *Alteration of hepatic function (no specific information provided): patients with chronic liver disease should not be given drugs to prevent preterm birth.*

Vital signs were also done as part of routine prenatal care but were not part of the clinical trial. Therefore, vital sign data were not submitted as part of the clinical trial database.

Medical Reviewer's Comments

- *The lack of routine vital sign data does not preclude a decision for approval based on efficacy or safety of this drug.*
- *Illnesses with significant vital sign changes such as preeclampsia were reported (see section 7.1.5.6, Table 22, Pregnancy Complications).*
- *Significant vital sign changes which warranted delivery of the patient or any other medical interventions were acted on by the managing clinician.*

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The applicant submitted very limited pharmacokinetic and clinical pharmacology information in non-pregnant and pregnant women. The final formulation, the labeled dose and duration of use, are identical to those used in the Phase 3 safety and efficacy trial. See Section 5 (Clinical Pharmacology) for an overview of data provided in this application.

There was no data submitted by the applicant regarding:

- In vivo drug interaction studies
- Quantitative in vivo metabolism
- Enzyme induction studies
- Studies examining the effect of intrinsic factors such as age, hepatic impairment, and renal impairment

Medical Reviewer's Comments

- *It would be useful to obtain additional drug metabolism and drug interaction information to provide clearer direction to optimize therapy. See recommendations in Section 5.1.*

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

As stated previously, 17α-hydroxyprogesterone caproate (17OHP-C) was approved by the Food and Drug Administration (FDA) in 1956 for use in pregnant women (NDA 10-347; Delalutin®). The approved indications included the treatment of habitual and recurrent abortion, threatened abortion, and post-partum "after pains." This approval was based largely on safety considerations in that it occurred prior to the FDA Drug Amendment of 1962, which required that drugs must have substantial evidence of efficacy in addition to evidence of safety in adequate and well-controlled trials. In 2000, the FDA withdrew approval for Delalutin. This action was taken at the request of the holder of the NDA because the holder was no longer marketing the drug. The action was not taken because of safety concerns.

In the Federal register published on Oct. 10, 1973, concern regarding the potential that progestins as a class are associated with congenital malformation was expressed:

- "Data have become available which suggest a possible association of prenatal hormone treatment of mothers with congenital heart defects in the offspring. The Food and drug Administration has reviewed available material and has presented the problem to its Obstetrics and Gynecology Advisory Committee. On the basis of these considerations it is concluded that a question of safety is raised by inferential evidence supporting the existence of an association between the administration of progestins during early pregnancy and the occurrence of congenital malformations. The potential risk of teratogenic effects is considered high enough to warrant removal of pregnancy-related indications from labeling of progestins currently marketed for systemic use. Those indications, some of which were evaluated as effective, and others, as probably or possibly effective are:
    - Presumptive test for pregnancy;
    - Treatment of threatened and habitual abortion; and
    - Treatment of any abnormalities of pregnancy including pregnancy complicating diabetes".

Subsequently, in the Federal register published on April 13, 1999, the recommendations outlined above were revoked:

- "The Food and Drug Administration (FDA) is proposing to revoke its regulation requiring patient labeling for progestational drug products. This patient labeling is required to inform patients of an increased risk of birth defects reported to be associated with the use of these drugs during the first 4 months of pregnancy. FDA has concluded that, based on a review of the scientific data, such labeling for all progestogens is not warranted".
- "The American College of Obstetricians and Gynecologists has objected to the progestational patient labeling requirement as applied to progesterone because there are no data to indicate that the use of progesterone causes any teratogenic effects, and the FDA warning is disturbing to infertility patients taking progesterone"

A discussion of potential long term safety issues with synthetic progestins is located in section 7.14., a single a case control study in adolescent males exposed to synthetic progesterone in-utero that showed a decrease in sex drive.

Medical Officer's Comments

- *The applicant submitted studies in the literature looking at adverse events which may be associated with progestins in general and with Delalutin® (17OHP-C) in particular. Although there is no evidence that this drug causes birth defects, the sponsor of the study (NICHD) decided to wait until 16 weeks gestation to begin therapy.*
- *This reviewer recommends that further case control studies should be done in the future to evaluate long term effects, especially of the reproductive system.*

7.2.8 Assessment of Quality and Completeness of Data.

The original intent of the NICHD MFMU Network was to conduct a study to determine if 17OHP-C was effective to reduce preterm births (less than 37 weeks gestation). The study was not specifically intended for drug approval. As such, adverse events were not captured in the typical manner used for studies designed to support a drug approval. Assessment of severity or relationship of AEs to study drug was not made for non-serious AEs. Adverse events that were considered serious or unexpected by the investigator were reported to the study sponsor and entered into the study database using the MFMU Network AE Form. This Form requested assessments of severity and relationship to study drug.

The infant follow up study was requested by the FDA several years after the sponsor completed the principal study. Only 14 of the original 19 centers were still participating. The sample of the follow-up children was one week older at birth in both treatment groups, thus not totally representative of the original population but still representative of the outcome of the original study..

Medical Officer's Comments

- *Despite the limitations of the data, this reviewer thinks the data are likely adequate to support approval of 17OHP-C in conjunction with the other recommendation described in Sections 1.1 and 1.2.2. These recommendations include both additional pre-approval and post-approval activities. Approval under regulation sub-Part H is an option. Post-approval studies should include a commitment to do another study to evaluate fetal wastage and a commitment to further evaluate long term follow-up of children at puberty.*
- *The Advisory committee concluded that the data submitted was adequate to evaluate safety pre-approval; however they recommended that the applicant conduct another study post-approval to evaluate the potential safety signal of increased miscarriages in the 17OHP-C arm.*

7.2.9 Additional Submissions, Including Safety Update

There are no ongoing trials that are being conducted by the applicant. Therefore, no other submissions are expected

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Miscarriages/Stillbirths (Possibly Related)

In the primary safety study (17-CT-002) there was a numerically higher incidence of both miscarriages and stillbirths in the 17OHP-C arm (see section 7.1.1). There was no increase in miscarriages or stillbirths in the supportive study 17-IF-001.

Injection Site reactions (Probably Related)

Injection site pain and swelling were the most common adverse events, with injection site swelling occurring significantly more often in the 17OHP-C group (see section 7.1.5.4). Injection site reactions were the most common reason for discontinuation (see section 7.1.3.1). Injection site reactions associated with vehicle resulted in almost 5% of subjects who received a "test injection" from entering the study (see section 7.1.5.6).

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Because the potency and quality of the recalled drug in the initial formulation study (17-IF-001) was in question, pooling of data across studies was not considered appropriate, and therefore was not done.

7.4.1.1 Pooled data vs. individual study data

Data were not pooled across studies (see section 7.4.1).

7.4.1.2 Combining data

Data were not combined across studies (see section 7.4.1).

7.4.2 Explorations for Predictive Factors

Based on the data provided, the only adverse reactions that appear to be drug related are injection site and allergic reactions. Therefore, no explorations for predictive factors were conducted.

7.4.2.1 Explorations for dose dependency for adverse findings

No explorations for dose dependency for adverse findings were performed because only a single dose was studied.

Medical Reviewer's Comment

- *See comments under section for recommendations*

7.4.2.2 Explorations for time dependency for adverse findings

Miscarriages by definition occur in a limited time frame. Gestational diabetes, preeclampsia, and oligohydramnios all usually occur later in pregnancy during the end of the second or third trimester.

In these studies, injection site reactions usually occurred soon after the first couple of injections; however the time of drop out of subjects from these reactions varied widely.

7.4.2.3 Explorations for drug-demographic interactions

Data comparing safety parameters in black vs. non-black subjects were reviewed. A few variables are worth mentioning:

Neonatal deaths: A higher percentage of black subjects had neonatal death in both the 17OHP-C arm (8/228 [3.5%]) vs. (2/158 [1.3%]) and the vehicle arm (7/126 [5.6%]) vs. (2/76 [2.6%]).

Injection and infusion site reactions: A higher percentage of non-black subjects had injection site and infusion site reactions in both the 17OHP-C arm (55.1%) vs. (37.1%) and the vehicle arm (51.3%) vs. (34.4%).

Medical Reviewer's Comments

- *The higher neonatal death rate in black subjects may be due to environmental factors. Treatment with 17OHP-C does not appear to be causative since the excess in black subjects is observed in both 17OHP-C and vehicle treated subjects.*
- *The lower percentage of injection site reactions in black subjects is an interesting finding. Perhaps melanin may confer greater tolerability to this drug and vehicle.*

7.4.2.4 Explorations for drug-disease interactions

Explorations for drug-disease interactions were not done.

7.4.2.5 Explorations for drug-drug interactions

Only a small of subjects received concomitant medications that were likely to either increase or decrease the metabolism of 17OHP-C. Consequently, no conclusions about drug interactions can be made.

Medical Reviewer's Comment

- *Selective drug-drug interactions studies will be recommended as a component of the studies recommended in the phase IV commitment.*

7.4.3 Causality Determination

Other than injection site reactions, this reviewer did not identify any other reactions clearly associated with the administration of 17OHP-C.

Medical Reviewer's Comment

- *A study to determine whether an increase in miscarriages/stillbirths is associated with 17OHP-C will be required as a post approval commitment. In addition, long term follow-up of children, perhaps a registry, will be recommended.*

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen was not supported by dose finding studies submitted in the Application. The dose of 250 mg/week is that used in several of the clinical studies for prevention of PTB reported in the literature. Most notably this was the dose proposed (b) (4) by Dr. Johnson at John's Hopkins University in 1974 and later reported in a publication (Johnson JW, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17 α-hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med. 1975;293(14): 675-80). Dr. Johnson's protocol was reviewed by the Obstetrics and Gynecology Advisory committee and his protocol was accepted by both the advisory committee and the FDA with one stipulation: the timing of the dose must occur at 16 weeks gestation or later to avoid structural anomalies of the fetus. Despite later research which did not confirm an association between 17OHP-C and birth defects, this timing and dose has became the common practice for the off-label use of 17OHP-C for prevention of PTB.

8.2 Drug-Drug Interactions

No drug-drug interaction studies were done (see Section 7.4.2.5).

8.3 Special Populations

All subjects in the two active treatment clinical studies were female and pregnant. Subjects with renal or hepatic compromise were not studied: these disorders are relatively rare among pregnant women.

8.4 Pediatrics

This drug will be for prevention of PTB only in reproductive-aged pregnant women. However, children who were exposed to this drug in-utero were studied (see section 7.1.12, special safety studies). As stated previously, this reviewer recommends further follow-up evaluations of exposed children.

8.5 Advisory Committee Meeting

The Advisory Committee for Reproductive Health Drugs met on Aug. 29, 2006 to discuss this application. The discussion was rigorous and many of the members of the committee struggled with what to recommend. In general, there was support for approval; however, there was a unanimous opinion that further studies for safety, and possibly effectiveness, should be conducted post-approval.

The questions and vote were as follows:

Questions to the Committee:

Adequacy of Clinical Data to Support Effectiveness
In general, the FDA requires an Applicant to submit two adequate and well-controlled clinical trials as substantial evidence of effectiveness for a new drug product. 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

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)?

- The Advisory Committee made multiple recommendations for further studies which can be summarized in the following bullets:
  - Studies to evaluate the potential connection between 17OHP-C and miscarriages/stillbirths
  - Long term follow-up studies (possibly a registry) of children exposed to 17OHP-C, including evaluation of reproductive health/genital development, fertility, and carcinogenic potential.

- Evaluation of potential maternal complications such as depression, and gestational diabetes.
- Elucidation of the pharmacokinetic and pharmacodynamic properties of 17OHP-C.

To summarize, the advisory committee was supportive of approving this drug primarily since there are no other available therapies for this major public health problem. However, there is strong opinion that **required** post-marketing studies are conducted, particularly to further assess safety. These recommendations would support approval under the sub-part H regulation because approval would be based on a surrogate of infant morbidity and mortality.

8.6 Literature Review

The published literature includes several studies evaluating the efficacy of 17OHP-C in preventing preterm birth (see Table 35). Not included in Table 35 is the publication by Meis PJ, Klebanoff M, et al. that was based on the finding from Study 17P-CT-002 (the primary study supporting the efficacy and safety of 17OHP-C in this NDA.)

Table 35 Published Studies of the Efficacy and Safety of 17OHP-C in Preventing Preterm Birth

Investigator	Drug:Dose	Entry Criteria	Design	Number of Subjects	Start Tx	Stop Tx	Outcome % PTB[A]	No. of SAB[B]
LeVine 1964[1]	17P[D]: 500 mg weekly vs. Placebo	3 SABs	RCT, DB[C] Placebo 1:1	17P: 15 Placebo: 15	< 16 wks	36 wks	17P: 7/15 (46%) Placebo: 10/15 (66%)	17P: 3/15 Placebo: 7/15
Papiernik-Berkhauer 1970[2]	17P: 250 mg q 3 days vs. Placebo	High preterm risk score	RCT Placebo 1:1	17P: 50 Placebo: 49	28 – 30 wks	8 doses	17P: 4.1%) Placebo: (18.8%)	No data
Johnson et al 1975[3]	17P: 250 mg weekly vs. Placebo	2 SABs or 1PTB + 1 SAB or hx 2 PTBs	RCT, DB Placebo 1:1	17P: 18 (4 cerclage) Placebo: 22 (3 cerclage)	Booking < 24 wks	37 wks	17P: 0/18 (0%) Placebo: 9/22 (41%)	17P: 3/23 Placebo: 0/27
Hauth 1983[6]	17P: 1000 mg weekly vs. Placebo	Active duty military	RCT, DB	17P: 80 Placebo: 88	16 – 20 wks	36 wks	17P: (6.3%) Placebo: (5.7%)	No Data
Yemini 1985[4]	17P: 250 mg weekly + cerclage vs. Placebo	Hx of 2 SABs or 2 PTBs	RCT, DB Placebo 1:1	17P: 39 (39 cerclage) Placebo: 40 (40 cerclage)	Booking (12.2 wks av.)	37 wks	17P: 5/31 16.1%) Placebo: 14/37(37.8%)	17P: 8/39 Placebo: 3/40
Suvonnakote 1986[5]	17P: 250 mg weekly vs. no treatment	Hx of 1 PTB or 2 late SABs	Non-randomized	17P: 36 No Rx: 39	16 – 20 wks	37 wks	17P: 5/35 (14%) No Rx: 19/39 (49%)	No Data

[A] PTB=Preterm Births

[B] SABs=Spontaneous Abortions; Data for this outcome obtained both from the original articles and a meta-analysis by Keirse (see citation No. 2 below).

[C] RCT, Randomized Controlled Trial, DB=Double Blind

[D] 7P = 17OHP-C

1 LeVine L. Habitual abortion. A controlled clinical study of progestational therapy. West J Surg Obstet Gynecol. 1964;72:30-6.

2 Papiernik-Berkhauer E. Double blind study of an agent to prevent pre-term delivery among women at increased risk. Ref from Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Brit J Obstet Gynaecol. 1990;97(2):149-5

3 Johnson JW, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17 α-hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med. 1975;293(14): 675-80.

4 Yemini M, Borenstein R, Dreazen E, Apelman Z, Mogilner BM, .Kessler I, et al. Prevention of premature labor by 17 α-hydroxyprogesterone caproate. Am J Obstet Gynecol. 1985;151(5):574-7.

5 Suvonnakote T. Prevention of pre-term labour with progesterone. J Med Assoc Thai.1986; 69(10):538-42.

6 Hauth JC, Oilstrap LC 3rd, Brekken AL, Hauth JM. The effect of 17 α-hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. Am J Obstet Gynecol. 1983;146(2):187-90.

Source: Prepared by Medical Reviewer.

Medical Reviewer's Comment

- *These studies varied in enrollment criteria, study design, length/dose of treatment and endpoints. However, all studies that enrolled subjects with a history of at least one previous PTB showed a reduction in PTD in the 17OHP-C arm. In addition, the LeVine study (enrolled subjects with three previous SABs) and the Papiernik study (enrolled subjects with a "high risk" score) showed a reduction in PTB in the 17OHP-C arm. The study that showed no treatment effect was the Hauth study, which enrolled women who were active duty military. There is no evidence that this occupation places women at risk for PTB.*

Johnson et. al. 1975

The study previously conducted that is most comparable to the MFMU Network trial was the double-blind randomized controlled trial conducted by Johnson et al in 1974 at Johns Hopkins University.[26] This study enrolled women with ≥ 2 preterm births, ≥ 2 spontaneous abortions, or a combination of both. Exclusion criteria included: absence of a viable intrauterine pregnancy; failure to enter the study before 24 weeks gestation; and failure to receive a minimum of 3 doses of the assigned medication. Subjects were randomized to receive 17OHP-C 250 mg IM weekly from enrollment into prenatal care until 37 weeks gestation. Cervical suturing was performed on patients thought to have cervical incompetence (4 in the treatment arm; 3 in the placebo arm). Four patients received isoxsuprine: 2 in the treatment arm; 2 in the placebo arm. Premature birth did not occur in any of the 18 patients receiving 17OHP-C; 9 of 22 patients (41%) receiving placebo had premature birth. The perinatal mortality rate in the 17OHP-C arm was 0% compared to 27% in the placebo arm: of the 7 placebo deaths, 2 were neonatal deaths and 5 were intrauterine deaths. The warning of the potential of progestins to cause births defects was published in the Federal Register prior to the completion of this study. Dr. Johnson submitted an IND to the FDA which contained the data published in this paper along with a protocol to continue the study. The Obstetrics and Gynecology advisory committee met and concluded the following: "The discussion indicated that Delalutin is effective in preventing the onset of premature labor and that the possible benefits outweigh the potential risks of teratogenic effects. The consensus of opinion was that studies of the type presented in this IND might be initiated but that therapy should not be instituted prior to 16 weeks gestation.

Medical Reviewer's Comment

- *The results of this study provide support for the effectiveness of 17OHP-C for prevention of PTB. The small size of the study (18 and 22 subjects in the 17OHP-C and vehicle arms), however, limits the strength of the findings.*

Cochrane Meta-analysis of 17OHP-C and Vaginal Progesterone

The Cochrane Collaboration in 2006 published a review of published and unpublished clinical trials in which progestogens were used for prevention of preterm birth (PTB).[29] A total of six randomized controlled studies were identified that met eligibility criteria for inclusion of the review; five comparing IM 17OHP-C to placebo[26, 27, 30, 31, 32] and one comparing vaginal progesterone to placebo.[31] The NICHD trial forming the primary efficacy trial for this NDA was one of the studies included.[27] One trial included subjects experiencing twin pregnancies; the remainder enrolled women at increased risk of preterm birth. Doses tested ranged from 100 mg/day by the vaginal route, to 250-1000 mg/week given IM.

A meta-analysis of the six studies was conducted to evaluate three primary outcomes: perinatal mortality, PTB <34 weeks, and major neurodevelopmental handicap at childhood follow-up. Secondary outcomes included eight measures of maternal outcome and 20 fetal/neonatal outcomes, including PTB <37 and <28 weeks. A total of 988 women were included in the meta-analysis from the six trials. No studies included long-term infant/childhood follow-up, so the third primary outcome could not be assessed.

There was no statistically significant difference in the rate of perinatal mortality between the treatment arms. In only one study, the one using vaginal progesterone, was it possible to evaluate the risk of PTB at < 34 weeks; this was statistically significantly reduced (RR 0.15, 95% CI 0.04 – 0.64). There was a statistically significant reduction in the risk of PTB at < 37 weeks (RR 0.65, 95% CI 0.54 – 0.79) calculated over all six studies. Other secondary, outcomes showing a statistically significant advantage of progestogens included birthweight below 2500 g (RR 0.63, 95% CI 0.49 – 0.81, based on four studies) and diagnosis of IVH (RR 0.25, 95% CI 0.08 – 0.82, based on the Meis study only).

Prespecified subgroup analyses were conducted looking at the effects of route of administration, dose administered, gestational age at treatment onset and plurality of the pregnancy. Both the vaginal and IM routes appeared effective at preventing PTB <37 weeks. The trial in twin pregnancies[2] failed to show efficacy at prevention of PTB in this high risk population. There appeared to be no effect of dose (weekly doses of < 500 mg were as effective as those > 500 mg) or time of treatment initiation.

The authors conclude that, while progestogens by either the vaginal (progesterone) or IM route (17OHP-C) is associated with a reduction in the risk of PTB <37 weeks, it is uncertain whether this finding is linked to an improvement in maternal and/or long-term infant health. There is insufficient information about the potential harms of progestogen therapy.

Medical Reviewer's Comments

- *None of these results confirmed that treatment with 17OHP-C or progesterone to prevent PTB leads to an improvement in neonatal morbidity or mortality.*
- *The findings from this meta-analysis support the need for conducting more safety studies.*
- *The difference in dose and timing of treatment appeared to result in the same outcomes overall.*

<u>Case Control Studies of Children and Adolescents Exposed to 17OHP-C</u>
In the 1940's to 1960's exogenous sex steroids became popular in preventing spontaneous abortion. 17OHP-C (Delalutin) was frequently used in the 1950's and 1960's. Due to the use of this hormone prenatally, limited opportunity arose for assessing the long-range impact on humans.

- 1984, Archives of Sexual Behavior - Patricia Kester: This case control study was designed (1) to determine whether exogenous prenatal exposure to 17 α-hydroxyprogesterone caproate (Delalutin) affects male recreational interests in boyhood and adolescence and male

psychosexual development and (2) whether total dosage, duration, and time of exposure has an effect on the previously mentioned variables. Subjects included 25 prenatally Delalutin-exposed adolescent males and 25 closely matched unexposed adolescent males. The duration of exposure ranged from 1-36 weeks with a median of 16 weeks; the median gestation month at initial administration was two weeks. Subjects were administered the Bender Visual-Motor Gestalt Test, the Draw-a-Person Test, the Rosenzweig Picture-Frustration Study for Adolescents, the Embedded Figures Test, and the Forer Structured-Sentence Completion Test. There was no significant effect on (1) the type of and direction of aggression expressed, (2) the need to conform to group norms of social behavior, (3) gender identity, (4) interests in sports, games, and rough-and-tumble play, (5) visual spacial ability, (6) interest in reading and the type of books selected, and (7) selection of television programs. However, Delalutin-exposed subjects spent significantly more time in the sedentary pursuit of watching television. Nonetheless, non drug related factors had a large influence on the amount of time spent watching television.

- 1980, Psychoendocrinology – Patricia Kester: Fifty eight young adult males exposed to one of four hormone regimens were matched against non-hormone exposed controls. Thirteen (13) of the subjects were exposed to synthetic progesterone. Subjects were interviewed for various aspects of psychosexual development, and administered the Bern sex-role Inventory (BSRI), the Guilford-Zimmerman Temperament Survey (GZTS), the Strong Vocational Interest Blank (SVIB) and the Embedded Figures Test (EFT). "Synthetic progesterone" exposed subjects had some sex atypical childhood behaviors and a lower rating of sex drive along with a later onset of intercourse in adulthood.
- 1968, British J of Psych - Katharina Dalton: Ninety (90) children whose mothers received antenatal "progesterone" were compared with matched controls to determine if the "progesterone children" had acquired any educational advantage over normal children. The progesterone had been administered to the mothers by intramuscular injections in dosages varying from 50 to 300 mg. daily for the "relief of toxaemic symptoms". More progesterone exposed children were breast-fed at six months, more were standing and walking at one year, and at the age of 9-10 years the progesterone exposed children received significantly better grades than controls in academic subjects, verbal reasoning, English, arithmetic, craftwork, but showed only average grades in physical education. The developmental and intellectual advantages were all related to the dose of progesterone received by the mothers, those receiving over 8 g. being related to earlier walking, standing and better school grades. The greatest intellectual advantage was noted in children whose mothers received progesterone before the 16th week of pregnancy.

Medical Reviewer's Comments

- *The results of these studies must be interpreted with caution since they are case control in design.*
- *The finding of a decreased sex drive in male adolescents exposed to 17OHP-C in the 1980 publication in Psychoendocrinology by Kester supports the recommendation by the advisory committee (see section 8.5) to obtain further information from adolescents exposed in utero*

to evaluate any long term effects on the reproductive system (physiologic or psychologic effects).

- *It is reassuring that despite several instances where these children have been evaluated, there has been no literature reports that have confirmed a potential association with malignancy or other serious adverse effects.*
- *The findings of increased intellectual advantages in 17OHP-C exposed children the 1968 British Journal of Psychiatry by Dalton is questionable to this reviewer. Recent studies have attributed breast feeding alone to improved school performance. In addition, the article that discussed advancement of milestones in the exposed infants did not say what the racial/ethnic composition of the subjects was. Milestones such as walking can vary widely among ethnic groups.*

8.7 Postmarketing Risk Management Plan

No specific postmarketing risk management plan is recommended at this time.

8.8 Other Relevant Materials

The Division of Medication Errors and Technical Support (DMETS) does **not** recommend the use of the proprietary name Gestiva. The primary concern relates to look-alike and sound-alike confusion between Gestiva and Sustiva. Sustiva was identified as a name with similar appearance and sound to the proposed name Gestiva. Sustiva contains efavirenz and is indicated for the treatment of HIV-1 infection. Additionally, DMETS reviewed the container labels, carton and insert labeling from a safety perspective. Several areas needing improvement were identified. These will be addressed during the next review cycle.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy
The results from Study 17P-CT-002 of 463 pregnant subjects with a history of prior spontaneous preterm deliveries show the following:

- The frequency of preterm birth <37 weeks gestation was statistically significantly decreased in the 17OHP-C treatment group compared to that in the placebo group (37.1% vs. 54.9%). The reduction in preterm birth <37 weeks was independent of race, number of qualifying preterm births, and gestational age of the qualifying preterm birth.
- The frequency of preterm births <35 weeks (point estimate of -9.4%, 95% CI [-18.7%, -0.2%]) and <32 (point estimate of -7.7%, 95% CI [-16.1.%, -0.3%]weeks gestation was statistically decreased in the 17OHP-C arm.

- There is consistency of PTB reduction across centers at <37 weeks and <35 weeks gestation; however, at <32 weeks there was a greater reduction of PTB in the 17OHP-C arm at the University of Alabama compared to all other sites.
- The prolongation of pregnancy, defined as the time from randomization to delivery or date last pregnant, was numerically longer, by a mean of 6 days, in the 17OHP-C group compared to the vehicle group. The mean gestational age at delivery was one week greater in the 17OHP-C group compared to the vehicle group (36.2 vs. 35.2 weeks); this was statistically significant at p=.031.
- Neonatal mortality was numerically lower in the 17OHP-C group, but the between-group difference was not statistically significant (2.6% vs. 5.9%).
- Overall mortality (fetal and neonatal combined) was similar across the two treatment groups (19 of 306 [6.2%] in the 17OHP-C group vs. 11 of 153 [7.2%] in the vehicle group).
- Composite neonatal morbidity (neonates with death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC) was numerically lower in the 17OHP-C group, but the between-group difference was not statistically significant (11.9 vs. 17.2).
- The percentage of infants weighing <2500 g was statistically lower in the 17OHP-C group compared with the vehicle group (27.2% vs. 41.1%). The percentage of infants weighing <1500 g was numerically lower in the 17OHP-C group (8.6% vs. 13.9%) but not statistically different.
- Use of tocolytic therapy and cerclage placement were not significantly different between the 17OHP-C and vehicle groups.

Medical Reviewer's Comments

- *It is important to note that the statistically significant reduction in preterm birth <37 weeks was independent of race, number of qualifying preterm births, and gestational age of the qualifying preterm birth. This generalizability increases the likely clinical significance of this finding and the usefulness of this drug. However, the possible lack of consistency of PTB reduction at <32 weeks across all sites is of concern.*
- *The Division was particularly interested in the preterm birth rate at gestational ages <35 weeks and 32 weeks gestation since these lower gestational ages correlate more closely with infant mortality or morbidity. The percentages of preterm births at these gestational ages in the 17OHP-C arm were statistically lower than those in the vehicle arm. The upper bound of the 95% confidence intervals (after adjustment for the interim analyses) did not cross zero, meeting the usual criteria for statistical significance. However, the level of statistical significance was not of the level that one would like to observe for an Application containing only a single clinical trial.*
- *The non-surrogate endpoint, the composite neonatal morbidity/mortality index, was numerically lower in the 17OHP-C group but this finding was not statistically significant. However, this was a post hoc analysis requested by the FDA and the study was not powered for this endpoint.*

- *The strength of the efficacy data relies on statistical significant reductions of PTB at <35 and <32 weeks gestation, surrogate endpoints which are thought by the advisory committee to predict reduction in neonatal mortality and morbidity. The results of studies in the literature (see section 8.6) provide further support for the effectiveness of 17OHP-C for prevention of PTB; however, the small size and variable entry criteria for these studies limit the strength of their findings.*
- *The major weakness of the this data is that it relies on a single multicenter study, with a possible inconsistency across sites.*

Safety conclusions - Studies 17P-CT-002 and 17P-IF-001

- There were no maternal deaths
- In the principal study (17-CT-002), there were twice as many neonatal deaths in the vehicle arm, which was most likely due to the increased percentage of preterm births. The similar gestational ages at delivery of the neonatal deaths in the two groups suggests that the gestational age-adjusted neonatal death rate would be similar for each group.
- In the principal study (17-CT-002) a numerical increase in miscarriages occurred in the 17OHP-C group compared to the vehicle group: five miscarriages out of 306 subjects, or 1.6% of pregnancies in the 17OHP-C group; no miscarriages of 153 subjects, or 0% in the vehicle group. The rate of stillbirths was also numerically higher in the 17OHP-C group (6 of 306 subjects [2.0%]) than in the vehicle group (2 of 153 subjects [1.3%]).
- The most common serious adverse events (SAEs) were congenital anomalies. The number and type of these anomalies appear evenly distributed over the treatment arms. This rate of anomalies is consistent with the background rate for congenital anomalies in the general population of 2-3%. Other SAEs were very few with no trends suggesting any relationship to the study drug.
- Injection site pain and swelling were the most common adverse events, with injection site swelling occurring significantly more often in the 17OHP-C group. Injection site reactions were the most common reason for discontinuation. Injection site reactions associated with vehicle resulted in almost 5% of subjects who received a "test injection" from entering the study.
- This reviewer identified three out of nine complications of pregnancy reported by the Applicant where the percentage of affected subjects was numerically greater in the 17OHP-C arm. The pregnancy complications were gestational diabetes, oligohydramnios, and preeclampsia.

Safety Conclusions - Study 17P-FU

- There was no difference between the 17OHP-C and vehicle groups in the percentage of children who scored below the cutoff for at least one developmental area of the primary endpoint, the ASQ. The percentages of children who scored below the ASQ cutoff in each of the individual 5 developmental areas were similar in the 17OHP-C and vehicle groups.

- Developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age mates in physical, mental, social/emotional, or speech development, was reported for a comparable percentage of children in the 17OHP-C and vehicle groups.

- The major weakness of this study is that it was planned and conducted five years after the end of the principal study, and five of the original 19 centers were no longer part of the MFMU Network. As such, the sample size had only a 50-60% power to detect an absolute difference of 10% and >80% power to detect a 15% absolute difference. One center (University of Alabama) contributed more than 30% of the subjects. Another weakness is that the data was primarily dependent on parental report. Ideally the ASQ screen positive children would have been followed up with a neurological exam and a formal psychometric exam (e.g. the Bayley's development scales).

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Overall Safety Summary

There are no definitive safety issues that have been identified. There is a suggested possibility of an increase in miscarriages or stillbirths. Injection site pain, swelling and pruritus are the most common reasons for discontinuation. There were no signals of developmental delay in the limited follow-up study of children. The safety findings require further study to determine their significance.

9.2 Recommendation on Regulatory Action

This reviewer recommends an approvable action for Gestiva [17α-hydroxyprogesterone caproate or 17OHP-C)] for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth. This recommendation is based on one multicenter clinical trial showing statistically significant reductions in preterm birth (PTB) at <35 and < 32 weeks gestation, surrogate endpoints recommended by an Advisory committee to predict reduction in neonatal mortality and morbidity. Additionally, although previous studies are small, the data from the literature consistently demonstrates a decrease in PTB when women with a previous PTB or miscarriage are treated with 17OHP-C.

Approval is contingent on the following:

- Reassuring data from a multi-generational reproductive toxicology study for 17OHP-C.

Approval is also contingent on the following as a post approval commitment:

- Safety studies to assess to potential association of 17POH-C with miscarriages/ stillbirths, and long term safety evaluations of children at age 18-24 months and during adolescence.
- Additional data to provide further statistical support for the effectiveness of 17OHP-C to reduce the incidence of preterm birth (PTB) particularly at <35 and <32 weeks gestational age.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

.No risk management actions are recommended at this time.

9.3.2 Required Phase 4 Commitments

Further study is needed to evaluate the following potential safety issues with 17OHP-C:

- The potential association of 17OHP-C with increased risk of second trimester miscarriage and stillbirth.
- Additional assessment of children at age 18-24 months whose mothers were treated with 17OHP-C including a screening assessment, and a formal psychometric assessment for those who screen positive, with an assessment by a neurologist.
- Long-term safety data from children (at least through puberty) whose mothers were treated with 17OHP-C, with a particular emphasis on the status of the reproductive system. These data can best be obtained through establishment of a surveillance program (e.g. a registry) to evaluate exposure effects in adolescents.

The Applicant will need to obtain more data to provide additional statistical support for the effectiveness of 17OHP-C to reduce the incidence of preterm birth (PTB) particularly at <35 and <32 weeks gestational age. Ideally, the study would also provide statistical support for the effectiveness of 17OHP-C to reduce morbidity and possibly mortality associated with PTB. The Division recognizes the challenges of such a study, particularly the use of a placebo/vehicle arm. The Applicant should discuss with potential investigators, either individually or in small groups, potential study designs that would provide further evidence of effectiveness of 17OHP-C. The content of these discussions should be fully documented, particularly whether investigators would be willing to participate in a clinical trial that included a placebo/vehicle arm. These discussions should be conducted with investigators within the Maternal-Fetal Medicine Network Units sites and with investigators who are not within this network. If a clinical trial with a placebo/vehicle arm is not feasible, based on discussions with potential investigators, the Applicant will need to explore the feasibility of other adequate and well-controlled clinical trial designs that could provide statistically significant information supporting the effectiveness of 17OHP-C in reducing the incidence of PTB at <35 and <32 weeks gestational age.

9.3.3 Other Phase 4 Requests

- In consultation with the clinical pharmacologist (Dr. Tran), the following studies are requested as part of a postmarketing commitment (see clinical pharmacology review):
    1. Characterize the pharmacokinetics of 17OHP-C and its metabolites in pregnant women (includes both plasma and urine concentrations) at several periods throughout the

pregnancy. Assess the 17OHP-C exposure response relationship via sparse sampling of all subjects.

2. Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on 17OHP-C pharmacokinetics.
3. Assess the effect of body weight on the pharmacokinetics of 17OHP-C using samplings specified in comment 2.
4. Examine the effect of hepatic impairment on 17OHP-C pharmacokinetics.

9.4 Labeling Review

Deferred to next cycle.

9.5 Comments to Applicant

Recommendations under Sections 9.3.2 and 9.3.3 should be conveyed to the Applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

All studies were reviewed and described in the main body of the review.

10.2 Line-by-Line Labeling Review

Labeling review will be deferred until the next cycle.

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/s/

Barbara D. Wesley
10/18/2006 05:39:02 PM
MEDICAL OFFICER

Scott Monroe
10/19/2006 05:06:37 PM
MEDICAL OFFICER
I concur with Dr. Wesley's conclusions and recommendation that NDA 21-945 (17 alpha hydroxyprogesterone caproate) is Approvable for prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth.

NDA: 21-945

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	X		
2) Is the clinical section of the NDA adequately indexed and paginated?	X		There is no linked index but it is workable.
3) Is the clinical section of the NDA legible?	X		
4) Is there an adequate rationale for selection of dose and dosing schedule?	X		There are no PK studies in pregnancy, which would be ideal; the dose is one that has been used in clinical settings previously.
5) Are the requisite number of adequate and well controlled studies submitted in the application?		X	There is only one adequate and well controlled study; given the seriousness of the clinical problem, we agreed to consider it.
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	X		
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?			(To be addressed by statistician)
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	X		
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?			N/A

ITEM	YES	NO	COMMENT
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division)?	X		
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	X		
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	X		
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?			N/A
14) Has draft labeling been submitted?	X		
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?	X		The requested infant follow-up study was submitted.
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

_____
Reviewing Medical Officer / Date

_____
Supervisory Medical Officer/Date

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/s/

Barbara D. Wesley
10/12/2006 02:46:54 PM
MEDICAL OFFICER

Scott Monroe
10/12/2006 05:43:44 PM
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