CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-945
Priority or Standard	Priority
Submit Date(s)	12 July 2010
Received Date(s)	13 July 2010
PDUFA Goal Date	13 April 2011
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:

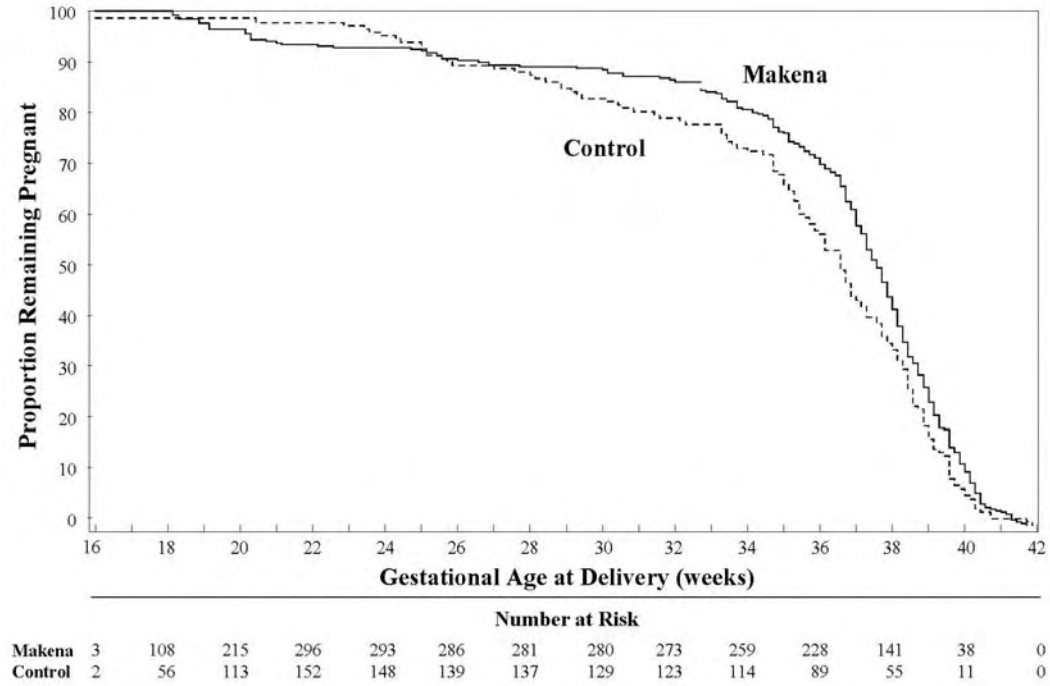
- *The strength of the efficacy data relies on statistically significant reductions of PTBs at <37, < 35 and < 32 weeks gestation. The reduction of PTB at < 37 weeks was the pre-specified surrogate endpoint and showed a statistically persuasive finding (p<0.001) of reduction in PTB. Despite the problems 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 (b) (4) 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.