

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21945Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 3, 2011
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	21-945 Complete Response submission (cycle 3)
Applicant	Hologic Inc.
Date of Submission	July 12, 2010
PDUFA Goal Date	April 13, 2011 (extended)
Proprietary Name / Established (USAN) names	Makena Hydroxyprogesterone caproate injection
Dosage forms / Strength	Intramuscular injection; 250 mg/ml once weekly
Proposed Indication(s)	To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth
Recommended:	<i>Approval</i>

1. Introduction

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

In 1998, the National Institute of Child Health and Human Development (NICHD) initiated a multicenter, double blind, 2:1 randomized, vehicle-controlled clinical trial through its Maternal-Fetal Medicine Units (MFMU) Network to evaluate the safety and efficacy of hydroxyprogesterone caproate (also known as 17- α -hydroxyprogesterone caproate or 17-HPC) in pregnant women with a history of spontaneous preterm birth. The initial trial (hereinafter referred to as 17P-IF-001) was terminated after about one year when the study drug was recalled by its manufacturer at the request of the FDA, due to violations of manufacturing processes that potentially could affect drug potency. At termination, only 150 of 500 planned women had been randomized, and only 86 women (57 17-HPC-treated women and 29 vehicle-treated women) had completed treatment.

A new trial was started (referred to as 17P-CT-002) and enrolled 463 of a planned 500 women before being terminated early due to crossing the prespecified threshold for efficacy as determined by the Data Safety Monitoring Board (DSMB). Results of the trial were published in the *New England Journal of Medicine* in June 2003¹. The American College of

¹ Meis PJ et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 348: 2379-85, 2003.

Obstetrics and Gynecology (ACOG) issued a Committee Opinion² in November 2003 stating that

...further studies are needed to evaluate the use of progesterone in patients with other high-risk obstetric factors, such as multiple gestations, short cervical length, or positive test results for cervicovaginal fetal fibronectin. When progesterone is used, it is important to restrict its use to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug.

However, this opinion was viewed as supportive of the use of 17-HPC for prevention of recurrent preterm birth, and use of compounded 17-HPC has increased substantially since 2003.

Adeza Biomedical obtained access to the NIH data in 2003 and began interactions with the Division regarding submission of a 505(b)(2) NDA. The original submission and the first Complete Response submission did not result in approval actions. The current submission represents the third review cycle for 17-HPC. Details of the prior review cycles and conclusions are outlined in Section 2.2.

In the third cycle review, new views in the scientific community about the importance of “late” preterm birth (i.e., between 34⁰ and 36⁶ weeks of gestation) led to a reconsideration of the utility of the prespecified efficacy endpoint and the manner in which Subpart H might be utilized to provide confirmatory evidence of efficacy for 17-HPC. This is discussed further in Section 13.2. In addition, due to the long period since 17-HPC had been marketed and the complexity of the review issues, it was decided to treat the application as would be an NDA for a new molecular entity (NME). For this reason, the signatory authority was transferred to the Office of Drug Evaluation III, and tertiary reviews have been filed by all disciplines.

2. Background

2.1 DESCRIPTION OF PRODUCT

The drug substance (17-HPC) was approved in 1956 under NDA 10-347 (with additional indications approved in 1972 under NDA 16-911) and marketed under the trade name Delalutin® for a variety of gynecological indications as well as for prevention of habitual, recurrent and threatened miscarriage. The Delalutin sponsor discontinued marketing in the 1990’s, and the NDAs were withdrawn “without prejudice” by the Agency in 2000. However, particularly since the publication of the 2003 New England Journal of Medicine article, 17-HPC has been compounded by pharmacists and used in women at risk of preterm birth.

Team Leader Comment:

Delalutin was not withdrawn from the market due to safety concerns, nor were efficacy concerns noted at the time of withdrawal.

² ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 291, November 2003

The proposed dosing regimen for the preterm birth indication is a weekly 1 mL intramuscular injection of 250 mg of 17-HPC in castor oil with 46% benzyl benzoate and 2% benzyl alcohol, beginning at 16 weeks 0 days (16⁰) to 20 weeks 6 days (20⁶ weeks) gestation and used through 36⁶ weeks gestation or birth.

2.2 REGULATORY HISTORY

2.2.1 Background and Material Reviewed in First Cycle Review

The original Applicant, Adeza Biomedical, submitted a preIND (68,108) application and met with the Division of Reproductive and Urologic Products (hereinafter referred to as DRUP or the Division) on January 30, April 5 and July 16, 2004 to discuss the submission of a 505(b)(2) application based upon the NICHD trial. Issues of concern that were conveyed to Adeza in these discussions included:

- The Division did not agree that adequate replicate evidence of the safety and effectiveness of 17-HPC for the prevention of recurrent preterm birth existed in the literature.
- Usually, either two adequate and well-controlled studies or a single study with a robust and compelling outcome and strong supporting data would be required to support approval of a new drug product. Data from the NICHD trial might not suffice to demonstrate the safety and effectiveness of 17-HPC.
- The utility of the published study's primary endpoint, reduction of preterm birth at <37 weeks of gestation; the Division believed that delivery at <32 weeks was more clinically important, as the majority of neonatal morbidity and mortality occurs in infants born at <32 weeks. In addition, the Division believed that demonstration of treatment benefit should focus on reduction of morbidity and mortality, rather than on increasing the gestational age at delivery without any associated clinical benefit.
- Absence of follow-up data of children exposed *in utero* to 17-HPC was noted; follow-up of at least 35-50% of exposed babies in each treatment arm through at least two years of age was requested.
- Data from Study 17P-IF-001 should also be submitted in the planned NDA, as should all literature addressing the use of 17-HPC for prevention of recurrent preterm birth.

A preNDA meeting was held on June 27, 2005, and the original application was submitted on April 20, 2006. The initial NDA submission provided pivotal safety and efficacy data from a single multicenter controlled trial (NICHD Study 17P-CT-002) to support the safety and efficacy of 17-HPC for the prevention of recurrent preterm birth. In addition, the Applicant submitted the data from the prematurely terminated initial efficacy and safety Study 17P-IF-001, and data from a follow-up study of infants delivered to mothers enrolled in 17P-CT-002 (this study is referred to as 17P-FU), which was conducted at the Division's request. Details of these three studies are summarized in Table 1.

Table 1 Clinical Studies of 17-HPC included in NDA 21-945

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

^A Study 17P-IF-001 was terminated early by the Sponsor when the manufacturer recalled the study drug. The last subject visit was in August 1999. Of the 150 subjects, 104 subjects (65 randomized to 17-HPC and 39 randomized to vehicle) had ended their treatment prior to the study termination either because they had completed treatment with study drugs (i.e., completed study treatment to 36⁶ weeks of gestation or delivery) or had withdrawn prematurely for reasons other than recall of study drugs.

^B An independent Data and Safety Monitoring Committee (DSMC) reviewed the study data after 400 subjects had completed the study. Based on that interim dataset, the primary endpoint, birth <37⁰ weeks of gestation in the 17-HPC group, was significantly reduced and the p-value was below the p-value specified in predefined stopping rules. The DSMC recommended that enrollment in the study be stopped, so that no new subjects would be assigned placebo. By the time enrollment was stopped, 463 subjects had been enrolled, which was 92.5% of the proposed sample size of 500 subjects.

Source: Based on final Study Reports.

2.2.2 Efficacy Results in First Cycle Review

Details on the demographics of the population enrolled in Study 17P-CT-002 are in the reviews of the original 2006 NDA. While there were no significant differences between treatment arms in the distribution of demographic and baseline characteristics, it is notable that almost 60% of subjects in both the 17-HPC and placebo arms were African-American. Distribution of the sample over the 19 participating MFMU Network centers was also of concern; some sites enrolled as few as two subjects, while the University of Alabama enrolled 27% of the total sample size.

Team Leader Comments:

- **Generalizability of the study results may be limited by the enrollment of African-American subjects at a rate far exceeding their distribution in the general population; however, the rate of preterm birth is higher in African-Americans than other ethnic groups in the US. In addition, subgroup analyses submitted during the first cycle did not indicate that race had a significant impact on efficacy.**

- **Heavy reliance on a single site for a large fraction of the study population is in contrast to stated characteristics³ of a single study that could provide adequate support for an efficacy claim. This is particularly problematic for the endpoint of preterm birth at <32 weeks gestation, as discussed below.**

The primary prespecified efficacy endpoint in Study 17P-CT-002 was percent of births at <37 weeks gestation. Additional endpoints requested by the FDA included percent of births at <35 weeks and at <32 weeks gestation, and a composite index of neonatal mortality and morbidity. The composite index was based on the number of infants who experienced any one of the following: death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis or necrotizing enterocolitis (NEC).

The primary efficacy endpoint was analyzed using the intent to treat (ITT) population. Outcome data were available on all women (except the four in the 17-HPC group who were lost to follow-up) even if they withdrew from treatment prior to delivery. Results for this and secondary endpoints, as calculated by the FDA Statistical Reviewer, are displayed in Table 2. The results at <37 weeks continued to favor 17-HPC when subgroup analyses categorized by gestational age of qualifying preterm birth, maternal race and number of previous preterm births were conducted.

Table 2 Efficacy Results: Percent with Preterm Delivery – Study 17P-CT-002

Gestational Age ^a	17-HPC ^a (N=310)	Vehicle (N=153)	Treatment difference [95% Confidence Interval, adjusted for interim analyses ^b]
	%	%	
<37 ⁰ weeks	37.1	54.9	-17.8%[-28%, -7%]
<35 ⁰ weeks	21.3	30.7	-9.4%[-19.0%, -0.4%]
<32 ⁰ weeks	11.9	19.6	-7.7%[-16.1%, -0.3%]
<28 ⁰ weeks	9.4	10.5	-1.1%[-7.4%, 5.2%]

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

^b To preserve the overall Type I error rate of 0.05, the adjusted confidence intervals (equivalent to a 96.6% confidence interval) use the final p-value boundary of 0.0345.

Source: FDA Statistical Review (First Cycle), Table 3.1, page 14, dated October 19, 2006 and FDA approved labeling, February 2, 2011

Team Leader Comments:

- **There was a statistically significant treatment effect of 17-HPC in preventing recurrent preterm birth at <37, <35 and <32 weeks, which remained consistent over varying levels of risk, as measured by maternal race, number of prior preterm births and gestational age of qualifying preterm birth.**
- **However, the rate of preterm birth at <37 weeks in the placebo group was higher than that typically reported in trials in a similar population (e.g., other trials within the MFMU Network). The rate in the 17-HPC group was more consistent with that typically seen in an untreated population.**

The Applicant also provided an assessment of the proportion of infants in each treatment arm who experienced one or more of the events making up the composite index endpoint of

³ Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998

neonatal morbidity/mortality. Although there was a lower proportion of subjects in the 17-HPC group (11.9% vs. 17.2% in the vehicle group) who experienced at least one event of the composite endpoint, this difference was not statistically significant.

Team Leader Comment:

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

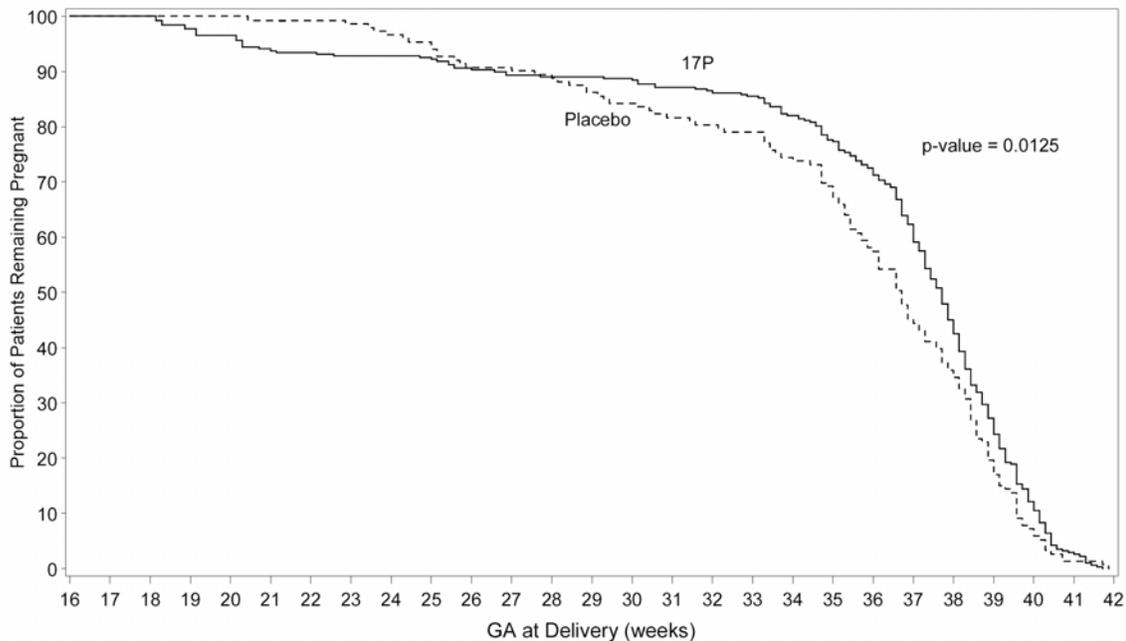
Individual components of the mortality/morbidity composite endpoint were also assessed, as were other secondary outcome measures, such as use of supplemental oxygen. Of 15 measures of neonatal morbidity evaluated, three were statistically significantly different, favoring a treatment effect for 17-HPC: use of supplemental oxygen (15% vs. 24%), any IVH (1.4% vs. 5.3%) and NEC (0 vs. 2.7%). There was also a numerical decrease in the neonatal mortality rate (2.6% in the 17-HPC arm vs. 5.9% in the placebo arm), but this was not statistically significant.

Team Leader Comment:

The analyses of individual neonatal morbidity endpoints were not adjusted for multiple comparisons and may not represent true treatment effects.

Pregnancy subsequent to the time of randomization was maintained for an average of six days longer in the 17-HPC group (131 vs. 125 days), with the mean gestational age at delivery being one week greater (36.2 vs. 35.2 weeks for 17-HPC and vehicle subjects, respectively). The Applicant provided a Kaplan-Meier analysis of the proportion remaining pregnant by week of gestation in the two arms of the study, which showed a statistically significant difference in the shape of the curves by the log-rank test (see Figure 1).

Figure 1 Proportion remaining pregnant, using staggered entry based on the gestational age at randomization – Study 17P-CT-002



Source: Applicant Response to FDA's request dated 7/20/06

Team Leader Comment:

The Kaplan-Meier curve demonstrates that the proportion remaining undelivered is higher in the 17-HPC group starting at about 28 weeks. Prior to about 26 weeks, however, the 17-HPC group has a higher rate of preterm delivery, attributable primarily to miscarriages and second trimester stillbirths (see Section 2.2.3).

Upon determination that the University of Alabama had contributed 27% of the sample size of Study 17P-CT-002, the Division requested that the Applicant provide a table analyzing the primary and key secondary endpoints for that single site, for all other sites and for all centers. Results are presented in Table 3.

Table 3 Percentages of Preterm Births at <37, <35, and <32 Weeks Gestation – Effect of Largest Center – Study 17P-CT-002

Gestation (weeks)	Percentage of Preterm Births								
	University of Alabama			All Other Centers Combined			All Centers		
	17-HPC (n=86)	Vehicle (n=40)	Diff.	17-HPC (n=224)	Vehicle (n=113)	Diff.	17-HPC (n=310)	Vehicle (n=153)	Diff.
<37	26.7	45.0	-18.3	41.1	58.4	-17.3	37.1	54.9	-17.8
<35	17.4	27.5	-10.1	22.8	31.9	-9.1	21.3	30.7	-9.4
<32	10.5	25.0	-14.5	12.5	17.7	-5.2	11.9	19.6	-7.7

Source: Applicant's submission of October 10, 2006

Team Leader Comment:

Although the rates of preterm birth at <37 and <35 weeks were lower in both the 17-HPC and vehicle arms in the University of Alabama subjects than in the subjects from the other centers combined, the treatment effect (i.e., the difference in preterm delivery rate between 17-HPC and vehicle arms) was comparable for the Alabama site and the other centers combined, suggesting a stable treatment effect across centers.

However, the rates of preterm birth at <32 weeks diverged from the overall study trend at the University of Alabama site – the preterm birth rate was higher in the vehicle arm and lower in the 17-HPC arm than in all other centers combined, leading to a much higher treatment difference at <32 weeks at the Alabama site than in all other centers and in the study as a whole.

The Applicant conducted several analyses to assess the possibility of a center effect, including an efficacy analysis with and without the University of Alabama site, a center-by-treatment interaction analysis using logistic regression, evaluation of consistency of treatment effect across centers using the Breslow-Day statistic and a stratified analysis controlling for University of Alabama vs. all other sites. The Applicant noted that the treatment differences at <32 weeks with (-7.7) and without (-5.2) the University of Alabama data were similar, as were the relative risks of birth <32 weeks (0.68 with and 0.70 without the University of Alabama data). The logistic regression analysis found no evidence of a treatment by site interaction. Results of the stratified analysis using the Cochrane-Mantel-Haenszel statistic showed that the treatment effect at < 32 weeks remained statistically significant (p=0.027) after adjusting for site. The remaining analyses were also interpreted by the Applicant to show little likelihood that the effect at <32 weeks was being “driven” by this single center.

Team Leader Comments:

- **Although the Applicant's analyses appear satisfactory, in the first cycle review, the large contribution to the total sample size by a single site for the <32 week outcome was of concern in an application that relied upon a single clinical trial to demonstrate efficacy at <35 and < 32 weeks of gestation.**
- **There were also exploratory analyses by the FDA Statistical Reviewer that suggested there might be an effect of the time of treatment initiation on efficacy: here again, disproportionate enrollment of women early in the eligibility window for gestational age at the University of Alabama might have impacted these results. These concerns further supported the first cycle decision that a confirmatory trial would be needed. However, the strength of the results in this trial were believed to be sufficient to support Subpart H approval, with the confirmatory results to be acquired postapproval. (See Section 13.1 for a discussion of how my thinking about single study and Subpart H approval has changed since 2006.)**

Although questions about the potency of the study drug used in Study 17P-IF-001 limit the reliability of its findings, the data were reviewed for efficacy and safety. There was no evidence of a treatment effect on the proportion of deliveries at <37 weeks (41.5% in the 17-HPC arm as compared to 35.7% in the placebo arm).

2.2.3 Safety Results in First Cycle Review

Subject disposition was comparable over the two study arms of Study 17P-002, with approximately 90% of each treatment group completing the study. Four subjects, all in the 17-HPC arm, were lost to follow-up. Of those withdrawing prematurely from the study, the percent due to an adverse event (AE) was 22% in the 17-HPC arm and 21% in the placebo arm.

There were no maternal deaths in either Study 17P-IF-001 or Study 17P-CT-002. Serious unexpected non-fatal adverse events occurred in three women and one infant exposed to 17-HPC. These included a postpartum pulmonary embolus, cellulitis at the injection site after the 8th injection, postpartum hemorrhage and respiratory distress after a 21 week stillbirth, and a male infant delivered at 37⁵ weeks with infarcted testicles secondary to intrauterine torsion.

The numbers of miscarriages, stillbirths, and neonatal deaths in each of the treatment groups are listed in Table 4. Five of 306 subjects assigned to the 17-HPC group experienced miscarriages. No subject in the vehicle group miscarried. The incidence of stillbirths was slightly higher in the 17-HPC group, but the difference was not statistically significant. Overall, eight subjects had stillbirths: six (2.0%) subjects in the 17-HPC group and two (1.3%) subjects in the vehicle group. The incidence of neonatal deaths was numerically twice as high in the vehicle group (5.9% vs. 2.6%, but the difference was not statistically significant. The overall incidence of fetal and neonatal mortality was similar in the two treatment groups ([6.2% in the 17-HPC group and 7.2% in the vehicle group).

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

Pregnancy Outcome	17-HPC N=306 n (%)^A	Vehicle N=153 n (%)^A	Nominal P-value^B
Miscarriages <20 weeks gestation	5 (2.4) ^C	0	0.17
Stillbirth	6 (2.0)	2 (1.3)	0.72
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.12
Total Deaths	19 (6.2)	11 (7.2)	0.69

^A Percentages are based on number of enrolled subjects and not adjusted for time on drug.

^B No adjustment for multiple comparisons

^C Percentage adjusted for the number of at risk subjects (n=211) enrolled at <20 weeks gestation.

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

Team Leader Comments:

- **A similar 17-HPC-associated increase in miscarriages and stillbirths was not observed in Study 17P-IF-001.**
- **However, a meta-analysis of four published studies⁴ also showed a possible association of 17-HPC with miscarriage, demonstrating a nonsignificant odds ratio of 1.30 (95% confidence interval 0.61 to 2.74).**
- **The similar gestational ages at delivery of the infants who died in the neonatal period suggests that there would be little difference in the gestational age-adjusted neonatal death rate between the groups. It appears that the decreased neonatal death rate in the 17-HPC arm is attributable to a lower proportion of early preterm deliveries as compared to the vehicle arm.**
- **There was no difference in the overall fetal/neonatal death rate between the two arms; the reduction in neonatal death in the 17-OHPC group was offset by the increased rate of fetal loss. Thus, there was no net survival benefit to offspring of women treated with 17-HPC in Study 17P-CT-002.**

Congenital anomalies were noted in 2% of each treatment group in Study 17P-CT-002, with a similar range of defects, including genitourinary and cardiovascular anomalies.

Team Leader Comment:

The general population background rate for congenital anomalies is 2-3%.

Discontinuation due to adverse events occurred in seven 17-HPC subjects and four vehicle subjects. Urticaria and injection site pain were the most common reasons for discontinuation (1% each).

The most common adverse events in Study 17P-CT-002 in the 17-HPC and vehicle groups, respectively, were injection site pain (35% and 33%), injection site swelling (17% and 8%), pruritis, including injection site pruritis (14% and 9%), urticaria (12% and 11%), nausea (6% and 5%), contusion (6% and 9%), and neonatal death (3% and 6%).

⁴ Keirse MJ. Progesterone administration in pregnancy may prevent preterm delivery. *Brit J Obstet Gynecol* 97: 149-54, 1990

Maternal complications were reported in both Studies 17P-CT-002 and 17P-IF-001. The proportion of women with three relatively common pregnancy complications (gestational diabetes, oligohydramnios and preeclampsia) was nonsignificantly higher in both studies in the 17-HPC arm as compared to the vehicle arm (see Table 5).

Table 5 Selected Pregnancy Complications: Studies 17P-CT-002 and 17P-IF-001

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

Source: Primary Medical Review (First Cycle), p 57, dated October 19, 2006, adapted from table 12-3 Final Report for Study 17-CT-002

Team Leader Comment:

All three of these complications are identified more frequently as pregnancy advances; therefore the apparent increased rates may be attributable to the prolongation of pregnancy in the 17-HPC arm, rather than to an adverse effect of the drug.

At the FDA's request, the Applicant conducted an infant/toddler follow-up study (Study 17P-FU) to provide outcome data at two years of age or greater on the children born to women treated in Study 17P-CT-002 (194 subjects exposed *in utero* to 17-HPC and 84 exposed to vehicle were enrolled). Details are provided in the clinical reviews of the 2006 submission. The primary objective of this study was to determine whether there was a difference in achievement of developmental milestones and physical health between children born to women who received 17-HPC compared with placebo during the pregnancy in Study 17P-CT-002.

There were no deaths in either group following discharge from the birth hospitalization. There were no differences between the two arms in the percent of children who scored below the cutoff (≥ 2 standard deviations below the mean) used to identify potential cases of developmental delay on the primary outcome measure, the Ages and Stages Questionnaire (ASQ) (27.5% in 17-HPC vs. 28.0% in the vehicle group).

Team Leader Comments:

- **The Applicant provided follow-up data on more than the 35-50% of the children that the FDA had specified as the minimal acceptable proportion of follow-up. The children followed were all at least 2.5 years of age, ranging up to 5 years of age.**
- **The mean gestational ages of the children in Study 17P-FU were one week greater than those seen in the total cohort of 17-HPC and vehicle-exposed children in Study 17P-CT-002. The participants in the follow-up study may therefore represent a slightly lower risk group than the original population.**
- **The rate of ASQ scores below the cutoff, signifying possible developmental delay, was higher in this study than would be expected based on normative data for the instrument. As vehicle-exposed children had a greater frequency of very low birthweight (<1500 gm) and delivery prior to 32 weeks, it would be expected that a**

higher proportion of vehicle-exposed children would be at risk for developmental delays on the basis of these perinatal risk factors. The classification of equal proportions (about 28%) of children in each group as possibly delayed suggests that the 17-HPC group also resembled an “at risk” group, albeit not as strongly attributable to low birthweight and gestational age. The Applicant did not conduct an analysis adjusting for these risk factors in assessing the proportion of possibly delayed children in each treatment group.

- **Based on this small number of children and the other assessments, there is no suggestion of adverse effects on postnatal development in the children whose mothers had been treated with 17-HPC during their pregnancy. There is also no indication that maternal treatment with 17-HPC resulted in any beneficial effect on early childhood development despite the prolongation of pregnancy and decrease in the rate of preterm birth; however, the study was not powered to detect such an effect.**

2.2.4 Recommendations of the Advisory Committee on Reproductive Health Drugs

The initial application was presented to the Advisory Committee on Reproductive Health Drugs (ACRHD) on August 29, 2006. A majority (13:8) of committee members voted that prevention of preterm birth <35 weeks was an adequate surrogate for a reduction in fetal/neonatal mortality and neonatal morbidity; the vote was nearly unanimous (20:1) that prevention of preterm birth <32 weeks was an adequate surrogate. Few committee members found prevention of preterm birth <37 weeks to be an adequate surrogate. A majority of members voted that the data submitted provided substantial evidence that 17-HPC prevents preterm birth at <35 weeks; a majority felt that there was not substantial evidence for effectiveness at <32 weeks.

The Committee voted unanimously that further study was needed to evaluate the potential association of 17-HPC with second trimester miscarriage/stillbirth; the majority (13:8) believed that this could be studied post-approval. The Committee also voted unanimously that additional trial(s) be conducted post-approval for further investigation of safety and/or effectiveness. Issues to be addressed in such a mandatory post-approval study included evaluation of the possible increased risk of miscarriage/stillbirth, assessment of possible maternal complications, and elucidation of PK and pharmacodynamic (PD) properties of 17-HPC. In addition, long-term follow-up (including reproductive development/function, fertility and carcinogenic potential of 17-HPC) would need to be obtained in a subsequent study or perhaps through use of a registry.

Team Leader Comments:

- **The data presented to the Advisory Committee for the rate of preterm birth at <32 weeks did not demonstrate statistical significance. Subsequent review and analysis by the FDA Statistical Reviewer concluded that the treatment effect of 17-HPC at <32 weeks was statistically significant. However, further analysis also elucidated that the significant result at <32 weeks may have been driven by a single center, which enrolled a disproportionate number of and racially non-representative subjects.**
- **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., birth <35 weeks of gestation. Since the time of the meeting, there has been reconsideration of this view, with new acknowledgement of the impact of “late” preterm delivery. This is discussed further in Section 13.2. For this reason, the Advisory Committee’s opinion on the value of the <37 week endpoint is**

no longer considered to reflect the current view held by obstetricians and pediatricians.

2.2.5 Conclusions of First Cycle Review

In the initial consideration of NDA 21-945, a major review issue was whether reliance for approval upon a single study that used a primary endpoint that is a surrogate for neonatal morbidity and mortality was justified. The clinical and statistical reviews raised questions as to whether the evidence of efficacy from this single study was convincing and compelling. My recommendation at the time (review dated October 20, 2006) was for an approvable action:

Therefore, I conclude that, while the Applicant has demonstrated efficacy of 17OHP-C in a single trial in reducing the risk of preterm birth at gestational ages that correlate with increased neonatal morbidity and mortality, these data are not sufficiently robust to support approval at this time. At a minimum, it needs to be determined whether a randomized, controlled confirmatory trial could be undertaken and successfully completed. Even if a placebo-controlled trial were not feasible, further study to determine the long-term safety of prenatal exposure to 17OHP-C, as well as to elucidate the signal of possible increased fetal mortality, is necessary.

The statistical reviewer, Lisa Kammerman, Ph.D., concluded in her review dated October 19, 2006, that

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

The clinical trial data did not provide evidence of a clinically meaningful or statistically significant effect on neonatal morbidity or mortality, as measured by a composite secondary endpoint. However, the trial did succeed in demonstrating efficacy of 17-HPC in preventing preterm birth at <35 and <32 weeks of gestation, cutpoints which the majority of members of the ACRHD believed represented adequate surrogates for fetal/neonatal mortality and neonatal morbidity. There remained some uncertainty as to whether the demonstrated benefit of 17-HPC in prevention of preterm birth at <32 weeks was due largely to the findings from a single large study site, or whether this result would be generalizable. There was also concern that the higher-than-expected rate of preterm delivery in the placebo arm of the study might be a factor in the efficacy demonstrated for 17-HPC.

In addition to lack of data on long-term safety of prenatal exposure, the clinical data suggested that there may be more immediate safety issues, particularly involving increased early fetal loss in women treated with 17-HPC, a finding that mirrors nonclinical data relating high doses of 17-HPC with increased embryoletality in mice, rats and monkeys. The increased early loss in the 17-HPC arm offset a decreased number of neonatal deaths, with the result that treatment with 17-HPC provided no net survival benefit.

Therefore, the Division concluded that, while the Applicant had demonstrated in a single trial the efficacy of 17-HPC in reducing the risk of preterm birth at gestational ages that correlate with increased neonatal morbidity and mortality, these data were not sufficiently robust to

support approval. Deficiencies were also identified in the Pharmacology/Toxicology and Chemistry, Manufacturing and Controls information provided in the submission.

An Approvable letter was issued October 20, 2006 that defined additional information required to obtain approval to market 17-HPC. The letter raised the possibility of eventual approval under Subpart H if the Applicant were able to address adequately the deficiencies noted in the first review cycle. The following deficiencies and possible remedies were outlined in the letter:

Clinical

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

Information needed to address the clinical deficiencies

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

Pharmacology and Toxicology

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

Information needed to address the toxicology deficiency

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

Chemistry, Manufacturing and Controls (CMC)

1. Significant degradation was observed for the light-stressed drug product sample with respect to content (assay) during the HPLC method validation studies. Thus, the drug product appears to be photosensitive; however, the resulting photodegradation products are not detectable by your HPLC method.

2. Given the results from your photostability study in which both the Stage 1 (fully exposed to light) and Stage 2 (enclosed in a chipboard box) samples showed decreases in content (assay) from that of the control (wrapped in foil) without corresponding increases in impurities by your HPLC method, you have not demonstrated that the secondary packaging provides adequate light protection for the drug product.
3. Your proposed expiration date of 24 months for the drug product is not acceptable based on the stability data included in your application to date.

Information needed to address the CMC deficiencies

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

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

Clinical

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

should have a formal psychometric assessment and an additional assessment by a neurologist.

Clinical Pharmacology

In planning your subsequent clinical trial(s), the following pharmacokinetic elements should be considered as part of the design to allow for better understanding of HPC pharmacokinetics and optimal dosing:

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

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

2.2.6 Background and Material Reviewed in Second Cycle Review

Confirmatory Safety and Efficacy Study

To address the clinical issues in the Approvable letter of October 20, 2006, the Applicant's Complete Response of April 24, 2008 contained the protocol for a confirmatory efficacy and safety study, along with a discussion of the likely feasibility of conducting the study. The Applicant also provided a draft protocol for an infant follow-up study, and a discussion of a proposed follow-up study of exposed offspring once they reached adolescence.

The Applicant proposed to conduct a multicenter, randomized, double-blind, vehicle-controlled study of 17-HPC for the prevention of preterm delivery in women with a previous singleton spontaneous preterm delivery. The study would enroll 1,707 women aged 16 and above with a singleton gestation, in a 2:1 ratio, stratified by study site, to 17-HPC or vehicle (hereafter referred to as placebo). Subjects would receive weekly injections of study drug from randomization at 16⁰ to 20⁶ weeks of gestation up through 36⁶ weeks or delivery. The same dose and formulation of 17-HPC used in Study 17P-CT-002 would be utilized. The vehicle would also be the same as that used in the previous study.

Eligible subjects would be women aged 16 years and above with a history of a prior spontaneous preterm delivery, with a current singleton pregnancy dated at the time of randomization at 16⁰ through 20⁶ weeks of gestation by ultrasound. Ultrasound between 14⁰ and 20³ weeks of gestation would be required to rule out fetal anomalies, which are exclusionary. Women with a history of thromboembolic disease, seizure disorder, hypertension requiring medication, current or planned cerclage, or taking heparin would also be excluded.

Subjects would receive a trial injection of placebo prior to randomization to evaluate for compliance and tolerability of the injection. Maternal subjects would be followed until the later of 30 days after last dose of study drug or discharge from the delivery hospitalization, and neonates would be followed until 28 days of life, with those remaining hospitalized at 28 days to be followed until the earlier of discharge or 120 days of life. Maternal subjects who discontinue study drug would remain on study, and, at a minimum, delivery outcome data would be obtained. A subject lost to follow-up would have the last date known pregnant noted for the analysis.

The primary efficacy endpoint would be the proportion of women in each treatment arm who delivered prior to 35 weeks of gestation, analyzed using the ITT population, and based on a staggered entry (adjusting for gestational age at enrollment) Kaplan-Meier analysis. If this endpoint attained statistical significance, the key secondary outcome of proportion of subjects in each arm who had a neonate with a score > 0 on the composite neonatal morbidity/mortality index would be evaluated.

Team Leader Comments:

- **The objectives and key endpoints were revised in accordance with comments made by the clinical and statistical reviewers, and were found acceptable in the second cycle review.**
- **The anticipated reduction in the <35 week delivery endpoint used to power the study was based on the results of Study 17P-CT-002 and appeared reasonable. Similarly, the expected rates of having a component of the neonatal index and of fetal/early infant death were based on Study 17P-CT-002 results.**
- **Dr. Lisa Kammerman, the FDA statistician who reviewed both cycles of the Gestiva application, indicated in her review addendum dated January 14, 2009 that she agreed with the changes made in the most recent protocol revision that address the statistical issues she raised in her review of the original protocol for the confirmatory study.**

Safety assessments would include determination of maternal AEs and protocol-defined pregnancy complications, including gestational diabetes, oligohydramnios, significant antepartum bleeding, preeclampsia and gestational hypertension, placental abruption and chorioamnionitis. Subjects would be asked a standard question to elicit AEs at each weekly visit. In addition, the safety outcome of rate of fetal/early infant death would be evaluated with a goal of excluding a doubling of risk in the 17-HPC arm compared to the placebo arm. The relationship, if any, between gestational age at randomization and risk of fetal/early infant death would also be assessed.

During the course of this review cycle, the ACOG issued a revised Committee Opinion on Use of Progesterone to Reduce Preterm Birth⁵. The new opinion was in contrast to the 2004 statement that stated

When progesterone is used, it is important to restrict its use to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug.

⁵ ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 419, October 2008

The 2008 opinion stated

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.

The Division interpreted this new statement as establishing a *de facto* standard of care for women with a previous spontaneous preterm birth, with little to no acknowledgement of the outstanding issues with regard to determining the safety and efficacy of 17-HPC. The Division was concerned that this opinion might make it extremely difficult for a physician to enroll patients into a placebo-controlled study.

Due to concerns about the impact of the recent ACOG opinion on the feasibility of the study, the Applicant was informed that the Division did not believe that the application provided sufficient evidence of feasibility of the confirmatory study. While the Applicant provided some reassurance that there remained US physicians willing to participate in the trial, the information provided did not address the probability of IRB approval or of patient enrollment. The Division concluded that adequate evidence of feasibility could only be addressed by actual initiation of the trial.

The Division agreed, in a teleconference on December 18, 2008, that a multinational trial would be acceptable, although inclusion of US and Canadian sites was requested.

Follow-up Study Proposals

In the Approvable letter, the Division had requested additional developmental assessment of children at ages 18-24 months whose mothers had been treated with HPC, including a formal psychometric assessment and an additional assessment by a neurologist for children who screen positive for developmental delay. In response, the Applicant provided an initial protocol for a non-interventional follow-up study of exposed offspring of mothers who participated in the confirmatory efficacy and safety study. The study would enroll 375 children (250 exposed *in utero* to 17-HPC and 125 to placebo) aged 18-24 months to determine whether there is a difference in the attainment of developmental milestones. Children would be evaluated using the Ages and Stages Questionnaire (ASQ), the same instrument used for screening in Study 17P-FU. Those who score positive for developmental delay in one or more of the five ASQ domains would be referred for further secondary evaluation (e.g., Bayley Scales of Infant and Toddler development, neurological exam, Gross Motor Function Classification System and Modified Checklist for Autism in Toddlers). The proposed sample size would be sufficient to provide 88% power to detect a 15% absolute difference in the rate of screen-positive subjects on at least one of the ASQ domains, based on an alpha level of 0.05 and an expected rate of 30% in the 17-HPC group.

Team Leader Comments:

- **The anticipated rate of screen-positive subjects in the 17-HPC was based on findings from Study 17P-FU, which found 28% were screen-positive for developmental delay on at least one domain of the ASQ. The proposed sample size is 25% greater than that in Study 17P-FU.**
- **The original follow-up Study 17P-FU was reviewed by a pediatric expert, (b) (4) (b) (4) during the first cycle. A number of her criticisms of the earlier study, including failure to follow-up screen-positive subjects with further appropriate evaluations and lack of neurological evaluations, were addressed in this protocol.**

- **If 17-HPC were approved in a subsequent review cycle, conduct of the follow-up study would be required as a phase 4 requirement. The Division requested that the Applicant seek to obtain consent to be recontacted for follow-up from all women eligible for enrollment in the confirmatory efficacy and safety study. From the pool of women who consent, formal consent for their child to participate in the follow-up study would be sought in the future, in a subset of sufficient size to provide a pool of 375 children who complete the ASQ assessment.**

The Applicant also discussed conducting a long-term post-treatment safety study; this was in response to the Division's request in the Approvable letter for long-term post-treatment safety data at least through puberty of exposed offspring.

Team Leader Comment:

The Division's original request for a long-term safety study was prompted in large part by the worrisome results concerning fertility and reproductive performance in the Pushpalatha nonclinical studies. Given the reassuring results of the new GLP-compliant reproductive toxicology study, the Division determined that there was not a current need to require such an adolescent study. If results of concern should be obtained in the infant/toddler follow-up study, the Division might decide to request a longer-term follow-up study under its FDAAA authorities, based on identification of a new safety signal.

2.2.7 Conclusions of Second Cycle Review

The Applicant had satisfactorily addressed the CMC and Pharmacology/Toxicology deficiencies raised in the first cycle review action letter. Following discussion with the clinical and statistical reviewers, the Applicant submitted an acceptable protocol for the Confirmatory study. Lisa Kammerman, Ph.D., the statistical reviewer, concluded in an addendum to her review dated January 21, 2009

Since completing my statistical review of the applicant's complete response to the approval letter for NDA 21-945, the medical division and I have had numerous discussions with the applicant regarding their draft study protocol...

As a result of these discussions, the applicant submitted a revised protocol on 12/12/08. I agree with the changes made to the protocol and do not have any additional statistical comments.

However, concern about the feasibility of the confirmatory efficacy and safety study led the Division to issue a Complete Response decision. The following deficiencies and possible remedies were outlined in the letter dated January 23, 2009:

Clinical

We acknowledge your commitment to complete a confirmatory study as a condition of approval under Subpart H CFR 314.510. Your draft clinical protocol...has adequately addressed our recommendations regarding such a confirmatory study. We are in agreement with the design of the trial, planned sample size, primary and secondary objectives, and the proposed analysis plan.

Clinical Deficiencies

1. You have not provided adequate documentation that it will be feasible for you to conduct and successfully complete the Confirmatory Study...We believe that adequate assurance of feasibility can only be addressed by actual initiation of the

trial.

2. Additional developmental assessment at ages 18-24 months is needed for children whose mothers participate in the Confirmatory Study. This information is needed to provide additional reassuring data that treatment of mothers with hydroxyprogesterone caproate does not have a detrimental effect on early infant/childhood development.

Resolution of Clinical Deficiencies

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. You will need to provide sufficient documentation that the Confirmatory Study can be initiated and is likely to be conducted successfully. Acceptable documentation 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 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/childhood 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.

The Applicant was also advised that, if the product were to be approved, the following issues would need to be addressed post-marketing:

- Initiate and complete the follow-up described in point 2 above
- Provide data characterizing the PK of 17-HPC and its metabolites in plasma and urine in pregnant women through different gestational stages
- Conduct an *in vitro* study in human hepatocytes to determine whether 17-HPC induces or alters the metabolic activity of CYP1A2, CYP2A6 and CYP2B6

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Barbara Wesley, stated in her review of the current application, dated February 3, 2011:

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 17 α -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, Tomashek 2007, McIntire 2008, Martin 2009, The Consortium on Safe Labor 2010). 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.

Team Leader Comment:

I concur with Dr. Wesley’s recommendation.

Dr. Wesley did not recommend any postmarketing risk evaluation and mitigation strategies. She noted that the Applicant has been notified of the need to conduct the following clinical studies as postmarketing requirements, and agreed to appropriate timelines:

- Completion of the Confirmatory safety and efficacy study
- Completion of a double-blind, controlled study to evaluate development in a sample of offspring from mothers enrolled in the Confirmatory study

Team Leader Comment:

I concur with Dr. Wesley’s recommendations regarding clinical studies that must be completed postmarketing.

3. CMC/Device

Complete Response, Cycle 2:

The primary Chemistry Reviewer, Donna Christner, Ph.D., made the following recommendations in her review dated December 22, 2008:

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

There were no recommendations for post-marketing commitments or risk management steps. Labeling recommendations made by Dr. Christner were incorporated into the labeling revisions proposed by the Division.

Complete Response, Cycle 3:

Dr. Christner made the following recommendations in her review dated December 1, 2010:

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have adequate information as required (the tradename is still under review by DMEPA, but is not a CMC issue). The final overall "Acceptable" recommendation has been made from the Office of Compliance.

Therefore, from a CMC perspective, this NDA is still recommended for APPROVAL as was recommended in Review #2 dated 22-Dec-2008.

A tertiary review was submitted by Terrance Ocheltree, Ph.D., R.Ph. on January 10, 2011. He concluded that:

I concur with the "Approval" recommendation from an ONDQA perspective and the absence of ONDQA related post marketing commitments.

3.1 General product quality considerations

The drug substance and drug product information was reviewed and found acceptable in the original review NDA 21-945, and no CMC changes were proposed in the first or this current Complete Response. Three CMC deficiencies were conveyed in the first cycle Approvable letter dated October 20, 2006:

- Develop a supporting method that can adequately detect and quantitate the potential photodegradation products
- Provide a description and justification for new packaging system to protect the drug product from light; revise the product labeling to state that vials should be protected from light
- Determine the cause of the out-of-specification results for particulates under accelerated conditions and, if necessary, consider a different container closure system

The Applicant submitted additional data regarding the potential for photodegradation, and the Division agreed in a teleconference on January 11, 2007 that there was no increase in photodegradants and therefore no need to develop additional tests, and that photosensitivity of the product would be addressed with package labeling. For the third point, the Applicant provided adequate information about the particulate matter found in the stability samples held under accelerated conditions (see Section 3.3).

3.2 Facilities review/inspection

Although the Office of Compliance issued an Acceptable overall recommendation for all the facilities involved during the second review cycle, the current Complete Response submission was received more than two years after those earlier inspections. For this reason, the current application was classified as a Class 2 resubmission, and the Office of Compliance reviewed the need for reinspection. The Office issued an overall Acceptable recommendation on October 26, 2010. This recommendation was based on District recommendation following reinspection of one site, and based on profile for three sites.

3.3 Other notable issues (resolved or outstanding)

Late in the second review cycle, the Applicant informed the Division that, due to errors in calculation, the reported particulate matter results were 10-fold lower than the actual values. New data were submitted for review, including both corrected calculations and additional stability data (up to 30 months on the primary stability batches and 24 months on the process validation batches). The particulate matter values were well within specification, albeit higher than originally reported, and the information was found to be acceptable.

An additional issue was raised in the second review cycle regarding microbiological stability once the product vial was penetrated. This was satisfactorily resolved (see Section 0) and the data found to support an in-use shelf life of five weeks after initial penetration of the vial.

There are no notable CMC issues in this third cycle review.

4. Nonclinical Pharmacology/Toxicology

Original Submission:

As noted, one of the primary deficiencies in the initial application concerned insufficient preclinical data to support approval; specifically, lack of a multigenerational reproductive toxicology study. Published studies^{6,7} reviewed in the initial cycle dosed pregnant Wistar rats on gestational days 1, 7 and 14, using intraperitoneal doses of 10 and 25 mg/kg. These data demonstrated decreased sperm motility, viability and count in the F₁ male generation, as well as a reduction in implantation sites and viable fetuses when F₁ males were mated with naïve females. The relevance of the study findings to human males exposed *in utero* to 17-HPC were questioned on the grounds of insufficient numbers of animals, use of unconventional species, different route of administration, lack of any PK/ADME data, lack of correlation between gestational timing of exposure and expected timing of human exposure and lack of developmental studies in exposed offspring.

However, in the absence of well-controlled preclinical data, these published data raised concerns about adverse effects on exposed offspring. The Approvable letter dated October 20, 2006 stated:

A GLP-compliant, multigenerational reproductive toxicology study needs to be performed, evaluating all stages of pregnancy during which dosing will be administered in humans. The study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including

⁶ Pushpalatha et al. Naturwissenschaften 91: 242-4, 2004

⁷ Pushpalatha et al. Naturwissenschaften 92: 385-8, 2005

learning, behavior and reproductive function, in offspring exposed in utero. At the time of a Complete Response submission to this Approvable letter, provide, at a minimum, an unaudited interim final report of the requested study.

Complete Response, Cycle 2:

The first Complete Response submission included a multigenerational reprotox study, which was audited by FDA inspectors and found acceptable. This study in Sprague-Dawley rats included reproductive phases 1 and 2 and a teratology phase, with dosing occurring on gestational days 8, 14 and 20; 17; and 6, 12 and 18, respectively. Phase 1 and 2 were designed to demonstrate effects of dosing before (phase 1) and after (phase 2) gametogenesis. Doses of 0 (vehicle control), 5, 25 and 150 mg/kg/dose were used. The study did not show any adverse effects on the health of dams, fetuses, offspring or second generation offspring. Specific findings included:

- No adverse effects on any F₁ fertility parameters or on the F₂ sex ratio or viability index (phase 1)
- No adverse effects on sperm percent motility, count or concentration, or percent abnormal (phase 1 and phase 2)
- No adverse effects on delivery (phase 2)
- Dose-related increase in traumatic lesions of the feet in offspring from medium and high dose groups. However, the pharmacology/toxicology reviewer accepted the Applicant's argument that these were not treatment-related, as these lesions did not occur in offspring of phase 1 animals, which received more injections.
- Comparable physical, developmental and behavioral evaluations of F₁ pups from control and all dose groups
- NOAEL of 150 mg/kg/dose

In addition a PK study was also conducted in Sprague-Dawley rats, using 5 or 150 mg/kg on gestational day 5. This demonstrated a T_{max} of 24 hours and a T_{1/2} of about six days.

The primary Toxicology Reviewer, Alex Jordan, Ph.D., with concurrence by Team Leader Lynnda Reid, Ph.D., made the following recommendations in his review dated October 14, 2008:

Recommendations on approvability: I recommend approval of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth.

Recommendations for nonclinical studies: None

Recommendations on labeling: Under Pregnancy: The pregnancy category should be changed (b) (4) to B.

Additional labeling recommendations made by Dr. Jordan were also incorporated into the labeling revisions proposed by the Division.

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Complete Response, Cycle 3:

No nonclinical studies were requested or submitted in the second Complete Response. Dr. Jordan noted one area of labeling that had not been revised in accord with his previous recommendations. He made the following recommendation in his review dated August 11, 2010:

I recommend approval of 17-alpha hydroxyprogesterone caproate for the prevention of recurrent preterm birth.

Dr. Jordan added an addendum on November 24, 2010 after the Sponsor had agreed to his proposed revisions of the pharmacology/toxicology sections of labeling:

The label for 17-alpha hydroxyprogesterone caproate for the prevention of recurrent preterm birth is satisfactory from the standpoint of pharm/tox.

A tertiary review was entered by Abigail Jacobs, Ph.D. on January 6, 2011. Dr. Jacobs noted

1. *I agree that there are no outstanding pharm/tox issues for this NDA.*

2. *I discussed some possible editorial changes to the carcinogenesis section of the labeling with the Division. The reviewer can address the suggestions as he sees appropriate.*

5. Clinical Pharmacology/Biopharmaceutics

Original Submission:

The original NDA submission was found acceptable by Clinical Pharmacology in 2006. Very limited PK data available at the time of the original submission demonstrated a C_{max} of about five days, and a $T_{1/2}$ of almost eight days. An *in vitro* enzyme inhibition study showed that 17-HPC slightly inhibited (by <40%) CYP2C8, CYP2C9 and CYP2C19, and inhibited CYP3A4 by almost 50%.

The Approvable letter of October 20, 2006 contained three Clinical Pharmacology issues to be addressed post-marketing, as noted in Section 2.2.5.

Complete Response, Cycle 2:

No new clinical pharmacology studies were submitted in the first Complete Response. Two new literature reports on the metabolism of 17-HPC supported the previous finding that the caproate ester remains intact as 17-HPC is metabolized. One report mentioned in-press results of an *in vitro* study showing that 17-HPC and its metabolites enter the fetal circulation. The Sponsor proposed to address the three issues noted above in the proposed confirmatory efficacy and safety study or by submitting results from an ongoing NIH PK study.

The primary Clinical Pharmacology Reviewer, Doanh Tran, Ph.D., stated the following in his review dated August 26, 2008 and in an addendum to the review, dated January 15, 2009:

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

The following phase 4 commitments were requested in the addendum to the review:

- *The sponsor will provide data characterizing the pharmacokinetics (PK) of 17 α -hydroxyprogesterone caproate (17-HPC) and its metabolites in plasma and urine in*

pregnant women throughout different gestational stages.

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

Labeling recommendations made by Dr. Tran were incorporated into the labeling revisions proposed by the Division; however, labeling negotiations were not completed in the second review cycle.

Complete Response, Cycle 3:

No additional clinical pharmacology data were included in the July 2010 submission. The primary Clinical Pharmacology Reviewer, Sandhya Apparaju, Ph.D., stated the following in her review dated December 9, 2010, which was cosigned by the Office Director:

NDA 021945/ SDN # 51 [submitted on 07/12/2010] is acceptable from a Clinical Pharmacology perspective provided that a satisfactory agreement is reached with the Sponsor regarding the labeling language.

The two Clinical Pharmacology Phase IV Commitments (PMC) listed below should be communicated to the sponsor as part of the NDA action letter:

PMC #1: Provide data characterizing the pharmacokinetics of hydroxyprogesterone caproate and its metabolites in plasma and urine in pregnant women throughout different gestational stages.

The timeline for PMC study #1 is as follows:

*Final Protocol Submission: June 30, 2012
Study Completion Date: June 30, 2014
Final Report Submission: November 15, 2014*

PMC #2: Conduct an in vitro study using human hepatocytes to determine whether hydroxyprogesterone caproate induces the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.

The timeline for PMC study #2 is as follows:

*Final Protocol Submission: June 30, 2011
Study Completion Date: March 31, 2012
Final Report Submission: July 31, 2012*

Team Leader Comments:

- **The post-approval studies requested in the current review cycle include two of the three originally requested by the Clinical Pharmacology reviewers. The third, evaluation of HPC exposure-response relationship and the effect of body weight on the pharmacokinetics of 17-HPC via sparse sampling, is being addressed in the ongoing confirmatory clinical efficacy and safety study.**
- **The information described in these bullets will be requested as phase 4 commitments. The Applicant may be able to obtain the requested information for bullet 1 from published results from an ongoing NIH study at the University of Pittsburgh or may need to conduct an additional PK study to comply.**
- **Specific descriptions of and timelines for the clinical pharmacology studies to be conducted as postmarketing commitments were modified somewhat in the letter sent to the Applicant notifying them of postmarketing requirements and commitments. See**

Section 13.4 for specifics about the protocols and timelines to which the Applicant agreed.

Dr. Apparaju completed an addendum to her review when final agreement on labeling was reached. On February 3, 2011, she stated

NDA 021945 is acceptable from a Clinical Pharmacology perspective.

The revised labeling for Makena as submitted on 02/03/2011 is acceptable from a Clinical Pharmacology perspective.

6. Clinical Microbiology

Clinical microbiology consults were submitted on June 19, 2008 and December 18, 2008. In the initial response, the reviewer, John Metcalfe, Ph.D., reviewed a major amendment made to the submission (change in (b)(4) process), and recommended approval on the basis of microbiological product quality. He noted that

The proposed changes to the (b)(4) sequence do not adversely affect the microbiological quality of the subject drug product. No additional (b)(4) microbial retention validation studies are necessary since there are no changes to the (b)(4) (b)(4) type.

Further review of the submission resulted in a request that the Applicant justify the requested five-week shelf life following the initial penetration of the multiuse vial. Cytoc provided data using the USP <51> Antimicrobial Effectiveness Testing method. The reviewer, James McVey, Ph.D., noted that

The preservative has better activity against Candida albicans after 30 months at room temperature than it did initially. Activity against Aspergillus niger is questionable but the test only requires stasis for the fungi so the product passes this test.

Dr. McVey recommended Approval of the product and concluded that the preservative system is adequate for the product's labeled use period after initial penetration of the vial.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

7.1.1 Confirmatory Efficacy and Safety Study

In the current Complete Responses submission, the Applicant has provided evidence of having initiated the required confirmatory efficacy study. The Applicant addressed the specific requirements outlined by the Division as follows:

- Document IRB approval for at least 15 sites in US and non-US: 43 US sites have received IRB approval, and 10 more are pending; 29 non-US sites have received Ethics Committee approval and 19 more are pending
- Enroll at least 5% of the total sample size (85 subjects): 89 subjects, or 5.2% have been randomized
- Enroll at least 15 US subjects: 82 US subjects have been randomized

- Agree to enroll at least 10% of the total sample from US and Canada: the Applicant agrees to this, and has already attained 48% of the goal (170 subjects) with the enrollment of 82 US subjects

Team Leader Comments:

- **The Applicant has recruited a diverse group of US sites, including academic centers, military medical centers and private practices. The Applicant anticipates that about half of all sites will be in the US and Canada. The Applicant has also engaged a specialty contract research organization to provide support in recruiting patients and referring physicians.**
- **The Applicant has received IRB approval at four Canadian sites and has also received approval in the Czech Republic (5 sites), Hungary (8 sites), Italy (4 sites), Spain (4 sites), and the Ukraine (4 sites).**
- **I believe that the Applicant has demonstrated the ability to enroll sufficient numbers of investigators and patients to have a high likelihood of successfully completing the study. I conclude that they have acceptably addressed the deficiencies relating to the Confirmatory study that were noted in the January 2009 Complete Response letter.**

As noted in the January 2009 Complete Response letter, the protocol for the Confirmatory study, as revised over the second review cycle, was acceptable to the Division. One additional request was made by the FDA statistician in preliminary comments for a requested meeting (subsequently cancelled by the Applicant) that were sent to the Applicant in December 2009 – to explore the effect of gestational age on outcome by using gestational age as a continuous variable, and to conduct this analysis using methodology that assumes a linear, (b) (4), effect on fetal/early infant death. The Applicant agreed to amend the Statistical Analysis Plan to comply with this request.

The primary objective of the study is to determine whether 17-HPC reduces the rate of preterm delivery prior to 35⁰ weeks as compared to placebo. The key secondary objective is to determine whether 17-HPC reduces the rate of neonatal morbidity/mortality, as measured by a composite index, as compared to placebo. This will be assessed in a hierarchical manner, to protect the type 1 error, only if the primary endpoint of delivery < 35 weeks attains statistical significance. The elements of the neonatal morbidity/mortality index are:

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

Additional secondary objectives include:

- Exclusion of a doubling of the risk of fetal/early infant death or stillbirth in the 17-HPC arm as compared to placebo
- Determination as to whether 17-HPC reduces the rate of preterm delivery prior to 32⁰ weeks as compared to placebo
- Determination as to whether 17-HPC reduces the rate of preterm delivery prior to 37⁰ weeks as compared to placebo

- Determination as to whether 17-HPC reduces the rate of stillbirths (including fetal losses) from 20 weeks of gestation on, as compared to placebo
- Determination as to whether 17-HPC reduces the rate of neonatal death as compared to placebo
- Evaluation of PK/PD parameters for 17-HPC in a subset of 450 subjects stratified by BMI

The planned sample size of 1,707 women (1,138 on active treatment and 569 receiving vehicle only) will provide 98% power to detect a 30% reduction (30% to 21%) in the rate of preterm birth at <35 weeks with an alpha level of 0.05%. The study will also have 90% power to detect a 35% reduction (17% to 11%) in the rate of the composite neonatal index, allowing for fetal loss occurring in 2.5% of the pregnancies. The power to rule out a doubling of risk of fetal/early infant death, assuming a rate of 4%, is 83%.

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

Team Leader Comment:

The analysis accounting for gestational age at the time of randomization will help address concerns arising from the exploratory analyses by the FDA Statistical Reviewer in the first review cycle that suggested there might be an effect of the time of treatment initiation on efficacy.

Fetal/early infant death/stillbirth is defined to include

- Delivery from 16⁰ through 19⁶ weeks of gestation (spontaneous abortion/miscarriage)
- Death occurring in previable liveborns (<24 weeks of gestation)
- Ante- or intrapartum death from 20 weeks of gestation through term (stillbirths)

Standard assessments to work up the etiology of fetal/early infant deaths will be utilized, including perinatal autopsy and placental pathology.

During the course of the third cycle review, further consideration of the Confirmatory study design was engendered by discussion with the FDA statistician and with the Director of the Office of New Drugs. Changes to the protocol and to the DSMB charter were requested by the Division in a teleconference on January 5, 2011:

- Add as a co-primary efficacy endpoint the neonatal morbidity/mortality index (in addition to the proportion of subjects with preterm birth < 35 weeks). This will allow the Confirmatory study to address the treatment effect on a true clinical outcome, as specified under Subpart H.
- Revise the DSMB charter to indicate that the Applicant or DSMB chair may request additional meetings to be held more often than annually if indicated by accumulating data.

The Applicant agreed on January 7, 2011 to revise the protocol and DSMB charter to incorporate these changes. Because this trial is being conducted as a PMR under Subpart H

requirements, the agreed-upon timeline specified that the revised protocol will be submitted by March 2011.

7.1.2 Infant Follow-up Study

The Applicant submitted the protocol for the infant follow-up study, and the Division reviewed it during and following the second review cycle. The Division agreed that it was acceptable in comments provided to the Applicant in December 2009.

The primary objective of the follow-up study is to determine whether there is a difference in developmental status between offspring of women who received 17-HPC in the Confirmatory study, as compared to those of women who received vehicle. Sufficient children will be enrolled to assure that approximately 375 children (250 exposed *in utero* to 17-HPC and 125 to vehicle) complete the Ages and Stages Questionnaire (ASQ), the same measure used in the initial infant follow-up study (17P-FU). Children who screen positive for developmental delay will be referred for additional follow-up using the Bayley Scales of Infant and Toddler Development and an evaluation by a pediatric neurologist. Mothers will be requested at the time of the Confirmatory study to consent to participation of their children at the age of 23 to 25 months, and informed consent will be obtained again when the child reaches the target age. The sample size should provide 88% power to detect an absolute difference of 15% in the rate of developmental delay using an alpha of 0.05, assuming a rate of 30% in the 17-HPC group.

Team Leader Comments:

- **The FDA statistical reviewer has recommended that all US/Canadian subjects should be requested to enroll their children in the follow-up study. The Applicant has committed to this, and has asked all eligible US/Canadian subjects to consent to inclusion of their children in follow-up. To date, 65 US subjects have consented.**
- **Dr. Kammerman also requested that the follow-up study be powered to rule out a doubling of the risk of developmental delay in the children expose to 17-HPC *in utero*. The Applicant has stated that, based on the 28% rate of screen positives on the ASQ in Study 17P-FU, the study will have 95% power to rule out a doubling of risk, and 80% power if the rate in the vehicle arm is as low as 18%. The Applicant proposes adding a secondary analysis to the SAP to determine the relative risk of the primary outcome and the 95% confidence interval (CI). If the upper bound of the CI is ≤ 2.0 , a doubling of risk will have been ruled out. I find this proposal acceptable.**
- **Dr. Kammerman and the clinical reviewers asked the Sponsor to consider enrolling subjects born to women who had been unblinded to treatment assignment, as it is possible that the reason for unblinding could be related to the child's health and developmental status. The Applicant noted that the Division's 2009 comments included a request to maintain the blind until completion of the follow-up study. The Applicant also stated that to date, only a single subject has required unblinding. Because such a change in inclusion criteria would require re-review of the protocol by the IRBs, and re-consenting of women who have already given initial consent, I agree that the follow-up protocol should remain as approved by the Division in 2009 with respect to exclusion of offspring of subjects who have become aware of their treatment assignment. The Applicant should provide information on subjects who were not eligible for participation in the follow-up study due to breaking of the treatment blind. If this were to constitute a sizable proportion of the population, this would be a significant review issue.**

During the third cycle review, as noted above, further discussions within CDER led to the

following additional requests from the Division relating to design of the infant follow-up study:

- Offer enrollment in the infant follow-up study to all subjects who enter the Confirmatory study. The Applicant noted that some study sites in the Confirmatory study had declined to participate in the follow-up study, and that there might be some limits (e.g., translation issues) on use of the follow-up instrument in certain foreign sites. However, allowing for these limitations, the Applicant agreed to offer enrollment to all subjects at sites that planned to participate in the follow-up study also, and estimated that 580 – 750 infants would likely complete the developmental questionnaire.
- Because this large expansion of the follow-up study would necessitate additional time for all subjects to reach age 2 and complete follow-up, the Applicant agreed to submit an interim final study report based on those offspring who have completed follow-up at the time the Confirmatory study is complete (planned to be December 2016). A final study report will be submitted approximately two years later, when all infants have completed follow-up.

The revised protocol for the follow-up study will also be submitted in March 2011.

7.1.3 Statistical Issues Raised in the Third Review Cycle

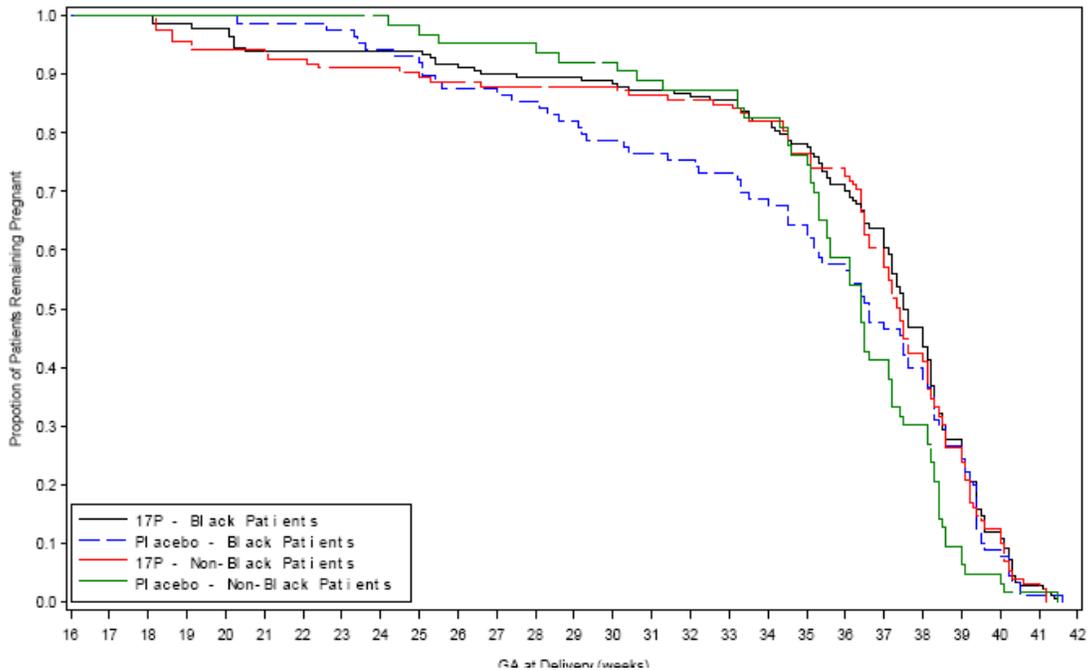
The FDA statistician, Lisa Kammerman, Ph.D. elected to conduct new exploratory analyses of the original data from Study 17P-CT-002 in the third review cycle. She raised the following new issues in her review dated February 3, 2011:

- Whether the efficacy and safety of 17-HPC varies by race, with African-American subjects having better outcomes than non-African-American subjects
- Whether the rate of early deliveries and fetal/early neonatal death is greater among women treated with 17-HPC than with placebo, and whether this varies by race
- Whether the treatment effect varies by gestational age at entry
- Whether results are confounded by study site, race and/or gestational age at entry

The Applicant conducted a number of additional analyses at the Division's request; these were submitted on February 2, 2011. Many of these analyses shed light on Dr. Kammerman's concerns.

Dr. Kammerman states that the advantage, in terms of Kaplan-Meier "survival" curves, emerged at 24 weeks for African-American subjects randomized to 17-HPC, but not until 35 weeks for non-African-American subjects on 17-HPC. However, this appears to be due to differences in the rates of delivery in placebo subjects, rather than to differences between races in the 17-HPC arms. This may reflect underlying risk status that varies between 17-HPC and placebo women. The Applicant's Kaplan-Meier analysis that simultaneously displays the proportions remaining pregnant in subgroups defined by race and treatment arm supports this (see Figure 2). The curves for African-American and non-African-American subjects on 17-HPC are superimposable, while those for placebo subjects of the different races show different, even crossing, trends in delivery.

Figure 2 Proportion Remaining Pregnant by Race and Treatment



Source: Applicant submission of February 2, 2011

Dr. Kammerman also claims that the fetal and early neonatal loss rate is equivalent among African-American subjects, regardless of treatment arm, but that the rate of such losses among non-African-American subjects is higher in those women randomized to 17-HPC than to placebo. The Applicant provided a table that indicated that the number of such losses in each cell is very small, and there does not appear to be a disparate trend by race (see Table 6).

Table 6 Miscarriages, Stillbirths and Neonatal Deaths by Maternal Race

Maternal Race	All			Black			Non-Black		
	17P (N=306)	Placebo (n=153)	Nominal p-value	17P (N=181)	Placebo (n=90)	Nominal p-value	17P (N=125)	Placebo (n=63)	Nominal p-value
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Miscarriages <20 weeks gestation	5 (2.4)	0	0.17	2 (1.5)	0	1	3 (3.9)	0	0.55
Stillbirth	6 (2.0)	2 (1.3)	0.72	3 (1.7)	1 (1.1)	1	3 (2.4)	1 (1.6)	1
Antepartum stillbirth	5 (1.6)	1 (0.6)	---	3 (1.7)	0		2 (1.6)	1 (1.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---	0	1 (1.1)		1 (0.8)	0	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.11	6 (3.3)	7 (7.8)	0.13	2 (1.6)	2 (3.2)	0.6
Total Deaths	19 (6.2)	11 (7.2)	0.69	11 (6.1)	8 (8.9)	0.45	8 (6.4)	3 (4.8)	0.75

Source: Applicant submission of February 2, 2011

Team Leader Comments:

- An examination of risk factors associated with these losses is informative. Although the list below includes all losses, only one of these – neonatal death in a 35-week infant – falls outside the category of “early losses.”
- In Table 7, I have characterized the losses as “explained,” “associated with preterm premature rupture of membranes (pPROM)” and “unexplained” deliveries. “Explained deliveries” include those induced for medical reasons. I consider it extremely unlikely that these deaths are related to study drug. The etiology underlying pPROM is not known, nor is it known whether or not 17-HPC has any impact on the frequency of pPROM. “Unexplained deliveries” are those that occurred without any known etiologic

factors; in these cases, it is most plausible that the loss could have a causal association with treatment.

- As might be expected, the proportion of all early losses attributable to “explained deliveries” was similar in placebo (18%) and 17-HPC arms (21%). Losses associated with pPROM were slightly more common among placebo subjects: 27% of placebo subjects with early losses vs. 21% of 17-HPC subjects. “Unexplained deliveries” accounted for 55% of placebo early losses, compared to 58% of 17-HPC early losses.
- Therefore, the rate of early losses that do not have other plausible explanations (and which therefore might be attributable to 17-HPC) in 17-HPC subjects does not appear greater than the rate of unexplained losses in placebo subjects.

Table 7 Risk Factors in Women with Fetal/Early Neonatal Losses

Subject ID	Treatment Arm	# Doses of Study Drug	Race	GA at Loss	Type	# Prior PTB	GA of Prior PTB	Comments
Losses with Underlying Explanations								
008-060	Placebo	5	AA	23 ⁶	Intrapartum stillbirth	2	35, 36	Delivery induced due to severe preeclampsia & placental abruption
002-015	Placebo	11	Non-AA	28 ⁰	Neonatal Death (Day 25)	2	29	Delivery induced due to severe preeclampsia
008-107	17-HPC	9	AA	25 ³	Neonatal Death (Day 6)	1	27	Delivery induced due to eclampsia
008-142	17-HPC	16	AA	35 ¹	Neonatal Death (Day 57)	2	29, 34 + 10 week miscarriage	Emergency C/S for uterine rupture
009-045	17-HPC	1	AA	20 ²	Neonatal Death (Day 1) Pre-viable fetus	2	34, 36	Bulging membranes with cervical dilation at randomization; delivery induced due to inevitable miscarriage
014-017	17-HPC	6	AA	25 ⁴	Neonatal Death (Day 197)	3	28, 29, 35 + 2 miscarriages	Delivery induced due to severe preeclampsia
Losses Associated with pPROM								
008-075	Placebo	4	AA	23 ⁴	Neonatal Death (Day 1)	1	26 + 10 week miscarriage	Delivery induced due to cord prolapse after pPROM
008-087	Placebo	9	AA	25 ¹	Neonatal Death (Day 2)	2	32, 32	pPROM with spontaneous delivery
008-091	Placebo	11	AA	28 ¹	Neonatal Death (Day 23)	1	34	Delivery induced due to pPROM & chorioamnionitis
004-048	17-HPC	1	AA	18 ¹	Miscarriage	1	22	Threatened abortion in first trimester; spontaneous delivery followed pPROM
008-114	17-HPC	3	AA	19 ¹	Miscarriage	1	26	pPROM & chorioamnionitis

Subject ID	Treatment Arm	# Doses of Study Drug	Race	GA at Loss	Type	# Prior PTB	GA of Prior PTB	Comments
015-014	17-HPC	3	Non-AA	18 ⁶	Miscarriage	1	21	Delivery induced due to pPROM
015-023	17-HPC	2	Non-AA	19 ¹	Miscarriage	1	20 + 16 week miscarriage	pPROM, chorioamnionitis
Unexplained Losses								
004-023	Placebo	4	AA	25 ⁰	Neonatal Death (Day 29)	1	32	
004-054	Placebo	2	AA	22 ⁶	Neonatal Death (Day 1)	3	31, 34, 36 + 16 week miscarriage	Pre-viable fetus
008-171	Placebo	3	AA	20 ⁴	Neonatal Death (Day 1)	1	33	Pre-viable fetus
015-032	Placebo	4	AA	23 ³	Neonatal Death (Day 1)	3	28, 31, 32 + miscarriage	Pre-viable fetus
013-005	Placebo	12	Non-AA	28 ⁶	Antepartum stillbirth	1	34	
013-026	Placebo	7	Non-AA	24 ²	Neonatal Death (Day 2)	2	35, 36 + 2 miscarriages	Delivery induced due to cord prolapse, preceded by preterm labor
008-102	17-HPC	2	AA	20 ²	Antepartum stillbirth	1	23	Delivery induced due to FDIU
004-035	17-HPC	3	AA	20 ¹	Neonatal Death (Day 1)	1	36	Pre-viable fetus
004-043	17-HPC	1	AA	20 ⁵	Neonatal Death (Day 1)	2	18 (twins), 27	Pre-viable fetus
015-022	17-HPC	1	AA	20 ²	Antepartum stillbirth	1	32	
017-011	17-HPC	1	AA	20 ¹	Antepartum stillbirth	2	29, 31	Spontaneous home delivery
008-110	17-HPC	1	Non-AA	18 ²	Miscarriage	1	36	Threatened abortion in first trimester; cocaine use during pregnancy
013-014	17-HPC	3	Non-AA	22 ⁴	Neonatal Death (Day 1)	2	20, 28 + miscarriage	Pre-viable fetus
014-012	17-HPC	1	Non-AA	21 ¹	Antepartum stillbirth	1	27	Delivery induced due to FDIU following pPROM & chorioamnionitis
018-024	17-HPC	5	Non-AA	22 ¹	Antepartum stillbirth	1	27	
021-033	17-HPC	6	Non-	24 ⁵	Neonatal	1	35	Placental "abruption" days to weeks pre-

Subject ID	Treatment Arm	# Doses of Study Drug	Race	GA at Loss	Type	# Prior PTB	GA of Prior PTB	Comments
			AA		Death (Day 10)		+ 9 week miscarriage	delivery
023-007	17-HPC	3	Non-AA	21 ⁰	Intrapartum stillbirth	1	22	

pPROM = preterm premature rupture of membranes; FDIU = fetal death in utero
Source: Applicant submission of February 2, 2011

Dr. Kammerman states that, overall, the rate of early deliveries – which mainly comprise miscarriages, stillbirths and early neonatal deaths (infants delivered prior to 24 weeks are considered nonviable, and, in fact, none survived) – is higher among 17-HPC subjects than placebo subjects. This is apparent in Figure 1, where the proportion remaining pregnant is higher among placebo subjects until approximately 25 weeks. However, the Applicant notes that this is due in large part to three losses among 17-HPC subjects very early in gestation, when the number of subjects at risk was low. Thus, these early losses/deliveries had a disproportionate impact on the Kaplan-Meier curves. Logistic regression analyses on the outcome of fetal/early neonatal death indicated that treatment arm, race and gestational age of earliest prior preterm birth were not significant predictors of fetal/neonatal loss. Only gestational age at randomization was a significant independent variable. This is likely because one of the fatal outcomes, miscarriage, is defined with respect to gestational age; thus, women randomized after 20 weeks were not at risk for miscarriage.

The patterns of enrollment were explored by race and treatment arm, and are displayed in Table 8. African-American subjects tended to enroll at slightly earlier gestational ages; the age at enrollment does not appear to vary greatly by treatment arm for either race.

Table 8 Gestational Age at Enrollment (Quartiles Enrolled) by Race and Treatment Arm

Mean GA at Enrollment (wks)	17-HPC		Placebo	
	AA	Non-AA	AA	Non-AA
1 st quartile	17.4	17.9	17.3	18.0
Median	18.4	19.3	18.7	19.1
3 rd quartile	20.0	20.4	20.0	20.3

GA = gestational age; AA = African-American

Source: Email communication from Lisa Kammerman, Ph.D., dated January 27, 2011

An examination of fetal/early neonatal losses by number of injections of study drug received is also informative. One might expect the number of such losses to increase with time in the study, a marker for longer time at risk for such events. This was observed in the placebo arm, where of 11 such losses, nine occurred in women who had been in the study long enough to have received > 3 doses of study drug. However, in the 17-HPC arm, 14 of 19 losses occurred in women who received ≤ 3 doses. In fact, 7 were in women who received only a single dose of 17-HPC. It is unlikely that a single exposure to 17-HPC would result in fetal/neonatal loss. As this scenario accounts for over one-third of the losses in the 17-HPC arm, I believe it does not support a causal association of 17-HPC with fetal/early neonatal loss.

Dr. Kammerman's subgroup analysis by gestational age at randomization suggested that the treatment effect was greatest among women randomized early (16-18 weeks), with no treatment benefit observed among women randomized after 20 weeks of gestation. She suggests that this also may be confounded by enrollment patterns that varied between African-American and non-African-American subjects, with African-American subjects tending to enroll earlier in gestation. Interestingly, however, it appears that the difference in delivery rate by gestational age is not in the 17-HPC subjects, all of whom showed similar rates of delivery < 37 weeks, regardless of gestational age at randomization, but in the placebo subjects. The delivery rate at < 37 weeks in placebo subjects ranged from 61% (in those randomized at ≤ 18 weeks) to 35% (in those randomized at > 20 weeks). Thus, the decline in treatment difference by gestational age at entry is not attributable to the impact of 17-HPC, but to the varying rates of preterm delivery among placebo subjects randomized early vs. late. This may reflect differential levels of risk among these subgroups.

The Applicant provided tables illustrating the distribution of two of the most important underlying risk factors for recurrent PTB (gestational age at earliest prior PTB and number of prior PTBs) by race and treatment arm. These showed that 17-HPC subjects of both races were more likely by 5-8% to have had earlier prior PTB than were placebo subjects. Conversely, the proportions of women with > prior PTB were higher in the placebo arms for each racial group than in the 17-HPC arms. Thus, the effect of underlying risk on treatment effect is not easy to characterize.

Regarding potential confounding effects, Dr. Kammerman found that racial distributions were not equivalent over study sites. This is not unexpected, given the geographic diversity of the MFMU Network. The Applicant conducted logistic regression analyses on two outcome measures – delivery < 37 weeks and “bad fetal outcome” defined as delivery < 32 weeks or fetal/early neonatal death. For both outcomes, the interaction terms of treatment by site, treatment by race and treatment by gestational age at randomization were not significant.

Team Leader Comments:

- **Dr. Kammerman bases many of her conclusions on Kaplan-Meier analyses, which present “time to delivery” or proportion remaining pregnant. However, it should be remembered that this was not the protocol-specified efficacy analysis; rather the specified analysis was evaluation of the proportion of subjects delivered at < 37, < 35 and < 32 weeks of gestation.**
- **Dr. Kammerman's exploratory analyses exclude the four subjects lost to follow-up. This is not consistent with the Applicant's methodology, which, conservatively, treated these women as delivered at the last gestational age to which they were followed. The impact of Dr. Kammerman's omission of these subjects is not known.**
- **The Confirmatory study will stratify subjects by gestational age at randomization. This will provide an appropriate study population in which to assess the impact, if any, of gestational age at initiation of treatment on the treatment effect.**
- **I believe Dr. Kammerman's exploratory analyses raise interesting hypotheses. The sample size of Study 17P-CT-002 is insufficient to draw conclusions based on these subgroup analyses, but these hypotheses should be further evaluated in the Confirmatory study, which is sufficiently large as to allow more powerful subgroup analyses.**

8. Safety

8.1 SAFETY FINDINGS

A summary of the safety findings from the original submission is presented in Section 2.2.3. No new clinical data were contained in this current submission.

8.1.1 Safety Update

A 120-day Safety Update Report was submitted on November 5, 2010; the Applicant reported on the ongoing 17-HPC clinical study 17P-ES-003. At the time of the safety report, 167 subjects had been randomized into the trial, and 59 had been consented to be contacted for the infant follow-up study (17P-FU-004) when their child reaches the age of two. Data is available on 88 subjects who had received the first blinded injection of study drug. Of 123 treatment-emergent AEs reported to date, the only ones that have occurred in more than two subjects are:

- Injection site pruritis (6)
- Injection site nodule (4)
- Nausea (4)
- Vaginal discharge (6)

One subject has discontinued due to an AE of rash at the injection site.

Team Leader Comment:

The reported AEs are consistent with those observed in the previous trial, and, aside from the injection site reactions, represent symptoms commonly observed in pregnancy.

There have been no maternal deaths. A total of 12 SAEs in eight subjects, three of which are neonatal or fetal deaths, have been reported. These include:

- pneumonia
- overdose (subject accidentally administered contents of entire 5-dose vial, without any apparent adverse effect)
- pancreatitis (with a recurrence ongoing)
- peripheral edema
- migraine and blood glucose increased
- neonatal cardiorespiratory arrest with neonatal death (delivery at 21 weeks, birth weight 340 gm)
- fall, premature rupture of membranes (PROM), intrauterine fetal death (32 weeks, tight nuchal cord documented)
- spontaneous abortion (19 weeks)

Narratives were provided for the three fetal/neonatal deaths. The delivery of the infant born at 21 weeks occurred 20 days after the start of study drug and was precipitated by preterm PROM and preterm labor. The mother presented with an elevated WBC. The infant had Apgar scores of 1 and 1 and lived less than 24 hours. The treatment blind has not been broken.

The 32 week IUFD occurred after the mother experienced a fall with spontaneous rupture of membranes, 84 days after starting study drug. She presented to the hospital with a viable

fetus and delivery was planned for 34 weeks. However, 6 days after admission, a repeat ultrasound revealed absence of fetal cardiac activity and labor was induced.

Details on the duration of study drug treatment for the 19 week miscarriage are pending.

Team Leader Comments:

- **The 21 week delivery may have been due to chorioamnionitis. The incidence of chorioamnionitis was not found to be elevated in women receiving 17-HPC in the initial trial.**
- **The relevance of a tight nuchal cord to IUFD is unclear. If additional information is available from placental and fetal examination, the etiology of the IUFD may be clarified.**
- **Overall, the limited data from the ongoing confirmatory study do not raise any new safety concerns.**

8.1.2 Postmarketing Safety Findings

The primary review by Dr. Barbara Wesley contains a review of current literature.

No country in the world has approved 17-HPC for prevention of preterm birth; thus, there are no postmarketing safety data on this product. However, the Division of Pharmacovigilance 2 was asked to provide an update on adverse event reports submitted to the AERS system since the previous review done in June 2008. These reports would be likely based on compounded formulations of 17-HPC. 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 also used alcohol during pregnancy (she described this as an “intense drinking problem”). She has filed a number of safety reports about this pregnancy to MedWatch.

Team Leader Comment:

Prenatal exposure to alcohol is associated with microcephaly, as is 8p monosomy. It is unlikely that these abnormalities are related to maternal use of 17-HPC.

8.1.3 Overall Assessment of Safety Findings

The safety concerns noted in the first cycle review remain pertinent. The proposed confirmatory efficacy and safety study will evaluate possible increased risk of early fetal loss and certain maternal complications (e.g., increased risk of gestational diabetes and preeclampsia). The infant follow-up study will evaluate possible long-term safety concerns relating to fetal exposure to 17-HPC.

9. Advisory Committee Meeting

As noted, an Advisory Committee was held in the first review cycle. This Complete Response application was not taken to an Advisory Committee.

10. Pediatrics

The Applicant requested a full waiver of pediatric studies, and the Division concurred, as studies would be impossible or highly impractical because there are too few children with the condition to study. The Pediatric Review Committee (PeRC), on September 10, 2008,

agreed to a partial waiver for premenarchal females, and to extrapolate efficacy for postmenarchal females.

11. Other Relevant Regulatory Issues

No financial disclosure information was submitted in this cycle, since no clinical efficacy data were provided.

During the first cycle review, site inspections at the three highest-enrolling sites were requested; per the Division of Scientific Investigation (DSI), none of the regulatory violations noted appeared to have a significant impact on data reliability or patient safety, and the data appeared acceptable to support the indication.

In the first cycle review, an audit of the non-clinical reproductive toxicology study site at (b) (4) was requested of DSI, in part because of the very different results of the submitted study and the published studies by Pushpalatha et al. In addition, the inspection evaluated corrective actions undertaken following an earlier inspection in April 2007. The audit was classified as No Action Indicated (NAI). Overall, there were no deficiencies that would affect acceptance of the (b) (4) data. No explanation for the difference in results from this study as compared to the Pushpalatha data was proposed beyond use of different rat strains and different days of first dosing.

12. Labeling

The trade name Gestiva had been found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) on October 22, 2008. However, in this third cycle review, the name was no longer acceptable to DMEPA due to concern about name confusion with the approved drug Sustiva. Several other names (b) (4) were submitted by the Applicant and found unacceptable by DMEPA. Ultimately, the name Makena was found acceptable by DMEPA.

The package insert and carton and container labeling was reviewed by DMEPA on October 25, 2010, and comments were conveyed to the Applicant. Final carton and container labeling was submitted by the Applicant on December 16, 2010, and found acceptable by DMEPA and the CMC reviewer.

The label was submitted in the format prescribed by the Physician Labeling Rule (PLR). Consults on the proposed label was obtained from the Study Endpoints and Label Development (SEALD) team, the Division of Drug Marketing and Advertising Communications (DDMAC) and the Division of Risk Management (DRISK). Their comments were incorporated into the label as appropriate. Major issues in the labeling review included:

- Clarification of the indication, with change from “prevention” to “reduction of risk” of preterm birth
- Development of patient labeling
- Inclusion of Subpart H language in the Indications section
- Clear description of the potential signal of increased early fetal mortality in the 17-HPC arm

- Discussion of the strength of the evidence for a treatment effect at < 37 weeks as compared to at < 35 and <32 weeks

Labeling agreement was reached with the Applicant on February 3, 2011.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

In the first review cycle, the Division concluded that criteria for approval on the basis of a single clinical trial had not been met, but that approval under Subpart H was a reasonable approach. In the current review cycle, my thinking has changed on two issues, which impacts my regulatory recommendation. First, I now appreciate that, where a single study is not found to be sufficient to support approval, Subpart H cannot be invoked in order to obtain the additional data needed for approval. Rather, Subpart H should be used to provide confirmatory evidence of a true clinical benefit, once there has been sufficient evidence from one or more trials to demonstrate a treatment effect on a relevant surrogate endpoint that is likely to predict a clinical benefit.

Second, there has been new appreciation of the burden of “late” preterm delivery (discussed further in Section 13.2), and, as a result, I no longer consider that the prespecified endpoint in Study 17P-CT-002 of delivery at < 37 weeks lacks clinical relevance. One of the main reasons 17-HPC was not initially approved on the basis of that single trial was that the Division was relying primarily on a demonstration of efficacy on the endpoints of delivery at < 35 and < 32 weeks. The statistical strength of the evidence supporting efficacy on these endpoints was not great, as evidenced by upper bounds that approached zero, indicating no treatment effect. However, for the endpoint of delivery at < 37 weeks, the statistical evidence is compelling ($p = 0.0004$), the confidence interval firmly excludes zero, and there is no concern that these data might be driven by the results obtained at the University of Alabama. I therefore conclude now that the evidence of efficacy of 17-HPC in improving the proportion of births occurring at < 37 weeks is both statistically compelling and clinically meaningful. For this reason, I now conclude that the evidence from Study 17P-CT-002 is sufficient to support approval of 17-HPC under Subpart H, on the basis of a single adequate and well-controlled trial.

I recommend that Makena receive an Approval action under Subpart H, 21 CFR 314.510 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.” This recommendation is based on data from a single study that demonstrated efficacy on a surrogate endpoint (delivery < 37 weeks) as well as on additional endpoints of delivery < 35 and <32 weeks. Subpart H 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, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed benefit to ultimate outcome. Postmarketing studies would usually be studies already underway.

I believe that approval under Subpart H is appropriate because the clinical trial data from Study 17P-CT-002 did not provide evidence of a clinically meaningful or statistically significant effect on neonatal morbidity or mortality, as measured by a composite endpoint. The efficacy endpoints (delivery at <37, along with delivery at < 35 and <32 weeks of gestation), on which statistical significance was demonstrated, are surrogates for neonatal morbidity/mortality. There remains a question as to whether the benefit of 17-HPC in prevention of preterm birth at <32 weeks (the strongest surrogate for a reduction in neonatal morbidity/mortality), was confounded by other factors (such as underlying risk status or gestational age at enrollment) or whether this result can be generalized. However, the evidence of efficacy in reducing the risk of preterm delivery at < 37 weeks gestation is compelling.

In the second cycle submission, the Applicant presented an acceptable protocol for a confirmatory efficacy and safety study, which the Applicant proposed to conduct post-approval. However, in view of a 2008 ACOG Committee Opinion, there was substantial concern as to whether the proposed study could be conducted in the US. At the end of the second review cycle, the Division concurred in the Applicant's proposal that the study be conducted globally, including in the US, in order to increase the likelihood that an adequate number of women would be enrolled and randomized and that the study would be successfully completed.

The Applicant has met this requirement to my satisfaction, and I believe it is now appropriate to proceed with approval under Subpart H. The Confirmatory study will be designed in a manner that should provide efficacy data on neonatal morbidity and mortality, the ultimate clinical outcome of interest. In addition, it will evaluate the potential safety signal of possible increased risk of fetal/early neonatal death. In this current submission, the Applicant has demonstrated that the Confirmatory study has been initiated. The Applicant also has acceptably demonstrated that it can enlist US physicians, that US IRBs have approved the study, and that US patients have consented to and are participating in the trial.

13.2 Risk Benefit Assessment

The public health importance of preterm birth and the lack of an approved efficacious treatment of preterm labor must be considered in weighing the risk/benefit ratio for a drug proposed for the indication of reduction of the risk of recurrent preterm birth. It was concluded by both the clinical and statistical reviewers in the first cycle review that the primary trial (Study 17P-CT-002) did not meet the general requirements for acceptance of a single adequate and well-controlled trial to provide sufficient evidence of efficacy to support approval of 17-HPC for marketing under 21 CFR 314.105. However, as noted in Section 13.1, I now conclude that there is sufficient evidence of efficacy in reducing the proportion of preterm births < 37 weeks of gestation to support approval, contingent upon provision of confirmatory data under Subpart H to show an actual clinical benefit.

My rationale for now accepting the endpoint of delivery at < 37 weeks as a clinically relevant surrogate endpoint is based on a body of literature that has been published, much of it subsequent to the Advisory Committee meeting in 2006. Since the time of the Advisory Committee consideration of this application, there has been considerable discussion in the literature and the obstetric community about the under-appreciated adverse effects of "late

preterm birth,” which is typically defined as delivery between 34⁰ and 36⁶ weeks of gestation⁸. As noted in a recent review article,⁹

There is now enough evidence that this population is not as benign as previously thought. They have increased mortality when compared to term infants and are at increased risk for complications including...respiratory distress syndrome (RDS), persistent pulmonary hypertension (PPHN), respiratory failure...Evidence is currently emerging that late preterm infants make up a majority of preterm births, take up significant resources, have increased mortality/morbidity, and may even have long-term neurodevelopmental consequences to their late prematurity.

This literature is discussed in greater detail in Dr. Wesley’s review.

Throughout the review cycles, the statistical reviewer, Dr. Lisa Kammerman, has recommended against approval of 17-HPC, even under Subpart H. In her current review, dated February 3, 2011, she states

From a statistical perspective, the information and data submitted by the Applicant do not provide convincing evidence regarding the effectiveness of 17 α -hydroxyprogesterone, caproate injection (17P) for the prevention of preterm deliveries among women with a history of at least one spontaneous preterm delivery.

The Applicant is seeking approval based on the results from only one adequate and well-controlled study, which has been submitted for review. The study, submitted with the original NDA, had several features that do not allow the study to stand on its own to establish the efficacy of 17P on the surrogate endpoint of preterm deliveries...

I do not agree with Dr. Kammerman’s view of the current level of evidence. Although the current data supporting approval come from a single trial using surrogate endpoints, I do consider Study 17P-CT-002 to have been an adequate and well-controlled trial. The surrogate endpoints of delivery rates prior to specified gestational ages all attained statistical significance, and the two lower gestational ages (35 and 32 weeks) were believed by a majority of members of the Advisory Committee to be reliable predictors of neonatal morbidity and mortality. I do acknowledge that Dr. Kammerman is particularly wary about the results at < 32 weeks, due to the possible influence of a single large study site on these results. However, I believe that the Applicant’s sensitivity analyses raise reasonable doubt as to whether the significant results at < 32 weeks are attributable to this single site.

Given this recent recognition of the significant impact of late prematurity, the Applicant’s strong statistical finding of treatment benefit in reducing the risk of delivery at < 37 weeks would now qualify this endpoint as “a surrogate endpoint that is reasonably likely...to predict clinical benefit” as defined under Subpart H. The treatment effect of 17-HPC showed a highly significant reduction ($p < 0.001$) in the risk of preterm delivery at < 37 weeks, by 18 percentage points from that observed in the control arm, with a confidence interval around the treatment effect that ranged from -28 to -7%. For this endpoint, the treatment effect observed in the University of Alabama site of concern was virtually identical to that in all

⁸ Engle WA. A recommendation for the definition of “late preterm” (near-term) and the birth weight-gestational age classification system. *Semin Perinatol* 30: 2-7, 2006

⁹ Ramachandrapa A, Jain L. Health issues of the late preterm infant. *Pediatr Clin North Am.* 56: 565-77, 2009

other study sites. It therefore appears that the endpoint on which the Applicant had the strongest evidence of efficacy is also one that is clinically meaningful in terms of predicting an improvement in overall neonatal outcome. The specific association of this reduction in preterm birth at < 37 weeks to the ultimate clinical outcome of morbidity and mortality will be further evaluated in the post-approval confirmatory trial.

Subpart H is essentially contingent approval, with FDA having the authority to rescind approval if the safety and efficacy of the drug is not upheld upon further study, and upon evaluation of endpoints that measure the actual clinical benefit desired. In addition, given the widespread use of compounded 17-HPC, I think it is of greater service to the public health to provide an FDA-regulated commercial product, with labeling that will promote safe use, than to delay approval for several more years awaiting completion of the confirmatory study.

13.3 Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are recommended.

13.4 Recommendation for other Postmarketing Study Requirements and Commitments

As 17-HPC is being approved for marketing under the conditions of Subpart H, 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.

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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), you 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

13.5 Recommended Comments to Applicant

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA M SOULE
02/03/2011

SCOTT E MONROE
02/03/2011

I concur with the recommendation of Dr. Soule to approve Makena under Subpart H regulations.