Advisory Committee Briefing Document

For

17 α-Hydroxyprogesterone Caproate Injection, 250 mg/mL

NDA 21-945

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Available for Public Disclosure without Redaction

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LIST OF ABBREVIATIONS

17-HPC	17 α-hydroxyprogesterone caproate (active drug substance of 17P)
17P	17 α-hydroxyprogesterone caproate injection, 250 mg/mL; contains 17 α-hydroxyprogesterone caproate 250 mg, benzyl benzoate, castor oil, and benzyl alcohol
ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
AE	adverse event
Apgar	score reflecting condition of newborn; based on appearance, pulse, grimace, activity, and respiration
ASQ	Ages and Stages Questionnaire
BMI	body mass index
BPD	bronchopulmonary dysplasia
CI	confidence interval
CT	completed study
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
FU	follow-up
IF	Initial Formulation
ITT	intent-to-treat
IVH	intraventricular hemorrhage
MedDRA	Medical Dictionary for Regulatory Activities
MFMU	Maternal Fetal Medicine Units
NDA	New Drug Application

NEC	necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NICU	neonatal intensive care unit
PDA	patent ductus arteriosus
pPROM	preterm premature rupture of membranes
PSAI	preschool activities inventory
PTB	preterm birth
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
SAE	serious adverse event
SD	standard deviation
SPTD	spontaneous preterm delivery
US	United States

1. EXECUTIVE SUMMARY

Treatment with 17 α-hydroxyprogesterone caproate injection, 250 mg/mL (17P) has been shown to significantly reduce the rate of recurrent preterm birth among women at high risk for preterm birth. In a controlled clinical study conducted by the National Institute of Child Health and Human Development (NICHD), weekly injections of 17P reduced the incidence of preterm birth and serious perinatal and neonatal morbidities. In 2003, the results of the NICHD study were published by Meis and colleagues in the *New England Journal of Medicine* and led to a recommendation from the American College of Obstetricians and Gynecologists Committee on Obstetric Practice that progesterone be used to prevent recurrent preterm birth.[1,2] At this time, no Food and Drug Administration (FDA)-approved formulation of 17P is available and the only source is from compounding pharmacies. Recognizing the benefits of having a product manufactured and marketed under FDA oversight, Adeza Biomedical (Adeza) has submitted a 505(b)(2) New Drug Application (NDA) submission to market GESTIVA (17P) for the prevention of recurrent preterm birth.

Preterm birth, defined as birth before the 37th week of gestation, is the leading cause of neonatal mortality and morbidity in the United States (US) and represents a major health problem.[3] The incidence of preterm birth continues to rise in the US. In 2004, the Centers for Disease Control and Prevention reported over 500,000 preterm births in the US, which equates to approximately 1 every minute. According to the Centers for Disease Control and Prevention, 12.5% of the 4 million births in 2004 occurred preterm, which represents an 18% increase since 1990 and a 33% increase since 1981.[4] There are multiple risk factors that increase the likelihood of a woman experiencing preterm birth including low prepregnancy weight, drug and alcohol abuse, non-Caucasian race, lower socioeconomic status, and medical complications during pregnancy. One of the most significant risk factors for preterm birth is previous pregnancy history, as women who have had a prior preterm birth have a 2.5-fold greater risk than women with no prior history of preterm birth.[5,6]

Infants born preterm are at increased risk of experiencing serious complications such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), periventricular leukomalacia, necrotizing enterocolitis (NEC), apnea, jaundice, anemia, and infections due to immature immune systems.[7,8] Preterm birth is also associated with significant long-term morbidities such as retinopathy of prematurity (ROP), cerebral palsy, and mental retardation. The increased risks of neonatal morbidities are apparent not only for those infants born very premature, but also for late preterm infants born at 34, 35, and even 36 weeks of gestation.[9,10,11]

The costs associated with preterm birth are staggering. The March of Dimes estimates that the hospital expenditures for preterm or low birth weight infants totaled $18.1 billion in 2003, which represents nearly half of all infant-related hospital spending.[12] The cost of inpatient and outpatient care throughout the first year of life for preterm infants is estimated to be 15 times that of term infants.[12] While neonatal hospital costs are higher on a per case basis for those infants born at the earliest gestational ages, total neonatal

costs are relatively consistent from 25 to 37 weeks because of the larger numbers of births with advancing gestational age.[13]

Currently, there is no effective FDA-approved product for preventing preterm birth. Despite widespread use, prophylactic methods, including pharmacological intervention, bed rest, and cervical cerclage have failed to demonstrate effectiveness in most studies.[14,15] Tocolytic drugs may be administered to reduce the frequency of uterine contractions after the onset of labor, but these drugs have not been demonstrated to prevent preterm birth.

Among the prophylactic interventions studied, progesterone agents have demonstrated the greatest potential to prevent preterm birth.[16,17] One such agent, 17 α-hydroxyprogesterone caproate (17-HPC), is a long-acting esterified derivative of the naturally occurring hormone 17 α-hydroxyprogesterone. 17-HPC has substantial progestational activity, a prolonged duration of action relative to its endogenous precursor, and no androgenic activity.[18,19] The safety of products containing 17-HPC as the active ingredient during pregnancy is supported by a long history of use, dating to the approval of Delalutin by the FDA in 1956. Delalutin was indicated for the treatment of habitual and recurrent abortion, threatened abortion, and postpartum after pains.

A number of historical clinical trials have shown the potential benefit of 17-HPC in preventing preterm birth in women at high risk for preterm delivery.[20,21,22,23,24] Among the 6 studies that examined the effectiveness of 17-HPC in preventing preterm birth in women with singleton pregnancies, 4 showed a significant reduction in the rate of preterm birth following treatment with 17-HPC.[21,22,23,24] Another study showed the same pattern of a reduced rate of preterm births with 17-HPC, but utilized a small sample size and appeared underpowered for statistical significance.[20] One study showed no benefit in using 17-HPC for prevention of preterm birth, but that study enrolled active military women who were pregnant, regardless of their previous pregnancy history.[25] A subsequent meta-analysis was performed by Keirse based upon the data from these 17-HPC clinical trials and confirmed the effectiveness of 17-HPC in reducing preterm birth.[16] In this meta-analysis, odds ratios demonstrated significant reductions in preterm birth, preterm labor, and birth weight <2500 g following 17-HPC use.

Although the individual studies and the meta-analysis supported a benefit of 17-HPC in reducing preterm birth, differences in methodology and treatment regimens in the individual studies did not allow for a consensus on the appropriate use of 17-HPC to prevent preterm birth. As a result, the Maternal Fetal Medicine Units (MFMU) Network of the NICHD designed and conducted a study to definitively evaluate the safety and efficacy of 17P for the prevention of recurrent preterm birth. The results from this study, hereafter referred to as Study 17P-CT-002, form the primary basis for the efficacy claim of Adeza's 505(b)(2) NDA submission.

The NICHD conducted a multicenter, randomized, double-masked, placebo-controlled study to evaluate the safety and efficacy of 17P for the prevention of recurrent preterm birth. This study enrolled a high-risk population of pregnant women between 16 weeks and 20 weeks 6 days gestation with a history of previous singleton spontaneous preterm delivery (SPTD). A total of 463 patients were randomized in a 2:1 ratio to receive weekly

injections of either 17P (310 patients) or placebo (153 patients) through 36 weeks of gestation or birth, whichever occurred first.

The results from this study confirmed the efficacy of 17P in preventing preterm birth. Treatment with 17P significantly reduced the incidence of preterm birth less than 37 weeks of gestation compared with placebo ($P<0.001$) (Table 1-1). 17P treatment also significantly ($P<0.05$) reduced the incidence of preterm births when defined as $<35^0$ or $<32^0$ weeks of gestation, significantly prolonged the duration of pregnancy from time of enrollment ($P=0.0024$), and significantly increased the mean gestational age at birth ($P=0.0024$).

Table 1-1. Summary of Efficacy Endpoints

Outcome	17P	Placebo	*P* value
ITT Data[a]	**N=310**	**N=153**	
Birth $<37^0$ weeks, n (%)	115 (37.1)	84 (54.9)	0.0003
Birth $<35^0$ weeks, n (%)	67 (21.6)	47 (30.7)	0.0324
Birth $<32^0$weeks, n (%)	39 (12.6)	30 (19.6)	0.0458
Prolongation of pregnancy, median days	131.0	125.0	0.0024
All Available Data[a,b]	**N=306[a]**	**N=153**	
Birth $<37^0$ weeks, n (%)	111 (36.3)	84 (54.9)	0.0001
Birth $<35^0$ weeks, n (%)	63 (20.6)	47 (30.7)	0.0165
Birth $<32^0$weeks, n (%)	35 (11.4)	30 (19.6)	0.0180
Mean gestational age at birth, wk	36.2	35.2	0.0024

Abbreviations: intent-to-treat (ITT)

[a] The ITT and all-available-data analyses included miscarriages, stillbirths, and patients lost to follow-up as treatment failures.

[b] Four patients in the 17P group were lost to follow-up (at 18^4, 22^0, 34^3, and 36^4 weeks of gestation) and were excluded from the all-available-data population. The results published by Meis and colleagues were based on the all available data.[1]

Treatment with 17P also led to significantly ($P<0.05$) lower incidence rates of low birth weight (<2500 g) infants, neonates with NEC, neonates having any IVH, neonates requiring supplemental oxygen, and neonates requiring admission to the neonatal intensive care unit (NICU) (Table 1-2). Although the differences did not reach statistical significance, incidence rates of RDS, ventilator support, and patent ductus arteriosus (PDA) were also reduced following 17P treatment.

Table 1-2. Summary of Infant Outcomes

Outcome	17P	Placebo	*P* value
All Available Infant Data[a]	**N=301**	**N=151**	
Mean infant birth weight, g	2760	2582	0.0736
Percent of infants <2500 g at birth, n (%)	82 (27.2)	62 (41.1)	0.0029
Percent of infants <1500 g at birth, n (%)	26 (8.6)	21 (13.9)	0.0834
Live Births	**N=295**	**N=151**	
Admitted to NICU, n (%)	82 (27.8)	55 (36.4)	0.0434
Necrotizing enterocolitis, n (%)	0	4 (2.7)	0.0127
Supplemental oxygen, n (%)	45 (15.4)	36 (24.2)	0.0248
Any IVH, n (%)	4 (1.4)	8 (5.3)	0.0258
Composite neonatal morbidity index, n (%)	35 (11.9)	26 (17.2)	0.1194
Mean days of respiratory therapy	1.7	2.7	0.0438
Integrated Data[c]	**N=404**	**N=209**	
Miscarriages, n (%)	6 (1.5)	1 (0.5)	0.2629
Stillbirths, n (%)	7 (1.7)	4 (1.9)	0.8769
Neonatal deaths, n (%)	10 (2.5)[d]	9 (4.3)[e]	0.1928

Abbreviations: neonatal intensive care unit (NICU); intraventricular hemorrhage (IVH)

[a] The all-available-data analyses included miscarriages and stillbirths as treatment failures.

[b] Four patients in the 17P group were lost to follow-up (at 18^4, 22^0, 34^3, and 36^4 weeks of gestation) and were excluded from the all-available-data population. The results published by Meis and colleagues were based on the all available data.[1]

[c] Integrated data include data from a terminated study initiated by NICHD prior to the definitive study. Details on this study and the integration of data are provided in Section 3.

[d] Percentage based on all randomized 17P patients; the rate for liveborn infants was 2.6% (10/386).

[e] Percentage based on all randomized placebo patients; the rate for liveborn infants was 4.5% (9/202).

The effectiveness of 17P treatment in the NICHD study was accompanied by a favorable safety profile. Weekly intramuscular injections of 17P were well tolerated by pregnant women, with injection site reactions being the most commonly reported adverse event (AE). *In utero* exposure to 17P was safe for the developing fetus and neonate as demonstrated by comparable rates of combined miscarriages, stillbirths, and neonatal deaths between the 17P and placebo groups, and rates of congenital anomalies identified at birth in the NICHD study (approximately 2% in both groups) that were consistent with those reported in general population surveys.

To assess the long-term outcome of infants exposed to 17P *in utero*, a follow-up observational study (Study 17P-FU) was conducted by the NICHD that examined the health and development of the infants born during the 17P-CT-002 study. This study was developed after completion of the 17P-CT-002 study and was specifically designed to assess safety outcomes. The study design was discussed with the FDA prior to initiation. This was a noninterventional safety study that collected data on children using the Ages and Stages Questionnaire (ASQ), a Survey Questionnaire tailored for this study, and a physical examination. The ASQ is a standard measurement tool completed by the

parent/guardian that evaluates development from 4 months to 5 years of age in communication, gross motor, fine motor, problem solving, and personal-social skills (see Appendix 1). The Survey Questionnaire was specifically designed for this study and collected information from the parent/guardian on the child's gender-specific play, physical growth, activity levels, motor control, vision or hearing difficulties, and any diagnoses since discharge from birth hospitalization that were made by a health professional. The physical examination included measurements of the child's current weight, height, head circumference, and blood pressure, as well as documentation of any major physical abnormality, with specific documentation for genital abnormalities.

The long-term follow-up assessments demonstrated no untoward effect of 17P on development or physical health. At the time of evaluation, children were between 2.5 and 5.4 years of age. Of the infants discharged from birth hospitalization, 68% of the infants in the 17P group and 59% of the infants in the placebo group were enrolled in Study 17P-FU. The demographics of the children were comparable between the 2 groups. There were no differences in the percentage of children with delay in at least one developmental area measured by the ASQ (communication, gross motor, fine motor, problem solving, and personal-social). The percentages of children with delay in each of the 5 developmental areas were also not statistically different. The data from the Survey Questionnaire did not identify any safety concerns related to the use of 17P during pregnancy. Physical examination findings included reports of genital or reproductive anomalies in 2.6% of the children exposed *in utero* to 17P and 1.2% of children exposed *in utero* to placebo. After a review of the study data and additional medical records for some of the children, no genital or reproductive anomaly was considered related to *in utero* exposure to 17P based on the physical finding, the gestational age at first exposure, or the presence of other likely contributing factors.

The safety of 17P during pregnancy is further supported by a number of published clinical and epidemiological studies. In the clinical trials examining the use of 17-HPC for prevention of preterm birth, 17-HPC exposure was not associated with neonatal deaths or the development of congenital anomalies.[20,21,22,23,24] Similarly, no adverse effects of 17-HPC on pregnancy outcomes or the developing fetus were observed in a study of threatened abortion.[26] Epidemiological studies have not shown an association between 17-HPC and the development of congenital anomalies. A study from the Mayo clinic examined a cohort of 24,000 pregnancies and found that the 649 offspring exposed to 17-HPC showed no increase in congenital anomalies compared with controls over a mean followup period of 11.5 years.[27] A collaborative cohort study of more than 13,000 women in West Germany included 462 first trimester exposures to 17-HPC and similarly found no increase in malformations.[28] In a study of 1608 infants born to mothers who received progestins during the first trimester, Katz and colleagues found no differences in the incidence of congenital anomalies, including genital anomalies, among infants exposed to progestins (including 17-HPC) compared with controls.[29] Overall, the results of these published studies support the NICHD study findings that 17P is not teratogenic and does not endanger the developing infant.

In conclusion, clinical studies demonstrate that weekly injections of 17P result in a substantial reduction in the rate of recurrent preterm birth among women at increased risk

for preterm birth, and also reduce the likelihood of clinically significant perinatal and neonatal morbidities. The administration of weekly injections of 17P is not associated with greater overall occurrences of adverse effects in pregnant women or any sequelae, including developmental delay in their infants, when compared with placebo. 17P is effective and has a favorable safety profile when used in the treatment of recurrent preterm birth in pregnant women.

The proposed indication for GESTIVA (17P) is for the prevention of preterm birth in pregnant women with a history of at least 1 spontaneous preterm birth.

2. INTRODUCTION

2.1 PRETERM BIRTH: UNMET MEDICAL NEED

2.1.1 Prevalence and Complications of Preterm Birth

Preterm birth, defined as birth before the 37th week of gestation, is a very serious health concern recognized as the leading cause of neonatal mortality and morbidity in the US.[3] In spite of advances in perinatal care, its incidence continues to rise in the US. According to the Centers for Disease Control and Prevention, 12.5% of the 4 million births in 2004 occurred preterm, which represents an 18% increase since 1990 and a 33% increase since 1981.[4] At its current rate, 1 preterm birth occurs nearly every minute in the US. In January 2003, the March of Dimes recognized this increase in preterm birth rate as a growing public health concern and started a multimillion dollar campaign to reduce preterm births as its primary initiative.

A number of factors have been identified that place women at-risk for preterm birth including previous pregnancy history, low prepregnancy weight, drug and alcohol abuse, non-Caucasian race, lower socioeconomic status, and medical complication during pregnancy. Women with prior preterm birth have demonstrated a substantially elevated risk (up to 2.5-fold higher).[5,6,30] Furthermore, the lower the gestational age of a prior preterm birth, the greater the risk of subsequent preterm birth. Mercer et al reported that women who delivered at 23 to 27 weeks gestation in a prior pregnancy had a 27.1% chance of delivering at less than 37 weeks in the current pregnancy.[5] When the prior delivery was at 28 to 34 weeks and 35 to 36 weeks, the probability for delivering before 37 weeks was 24.0% and 20.9%, respectively.

The NICHD has noted that a reduction in preterm delivery will reduce one of the primary causes of perinatal and neonatal morbidity and mortality.[7] Complications in the neonatal period that can occur with prematurity include RDS, IVH, periventricular leukomalacia, NEC, apnea, jaundice, anemia, and infections due to immature immune systems.[7] Long-term morbidities associated with preterm birth include retinopathy of prematurity, mental retardation, and cerebral palsy, which is 40 times more likely to occur in preterm infants than term infants.[30] Additionally, preterm infants without obvious neurological deficits remain at increased risk for cognitive problems such as attention deficit disorders throughout childhood.[10]

Preterm births impart a substantial financial burden on the US healthcare system. In evaluating the costs of preterm birth, Gilbert et al estimated the neonatal hospital cost for a preterm infant born at 25 weeks of gestation in California in 1996 was $202,700.[13] By contrast an infant born at 38 weeks of gestation would incur neonatal hospital costs of only $1100. The March of Dimes estimated that the total US hospital expenditures for all infants in 2003 was $36.7 billion, of which nearly half, $18.1 billion, was for preterm or low birth weight infants.[12] The average hospital stay for infants with any diagnosis of prematurity or low birth weight is 13.6 days compared with 2.0 days for term infants without complications. While these costs are primarily attributable to increased hospital stays during the neonatal period, the cost of inpatient and outpatient care throughout the

first year of life for preterm infants is estimated to be 15 times that of term infants.[12] Additional estimates have reported prematurity and low birth weight combined to account for 35% of all direct infant care expenditures in the US.[31]

The benefits of prolonging pregnancy by even 1 week are considerable. Along with birth weight, gestational age is one of the most important determinants of an infant's likelihood of survival and subsequent health.[3] Among extremely low gestational age infants, the chances for survival increase dramatically with each additional week of gestation.[32,33] In addition to neonatal mortality, major neonatal morbidities are also decreased with increasing gestational ages. Incidence rates of PDA, NEC, and IVH are known to markedly decrease with increasing gestational age up to 32 weeks, while incidence rates of respiratory distress syndrome and the need for ventilator assistance have been shown to decrease with gestational age up to 37 weeks.[13,34] Lastly, as shown in Figure 2-1, each additional week of gestation from 25 to 37 weeks is associated with reduced neonatal hospitalization stays and associated costs.

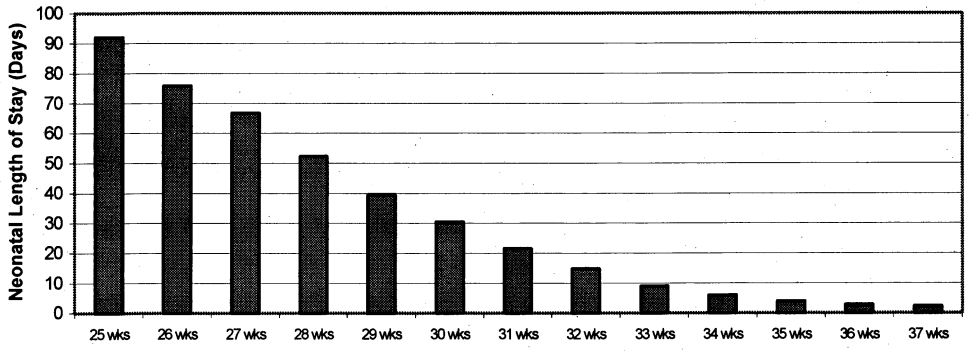


Figure 2-1. Neonatal Length of Hospital Stay by Gestational Age

The neonatology literature has historically focused on the outcomes of very low birth weight (<1500 g at birth) or very preterm infants, a population with the highest rate of mortality and morbidity.[32] Recently, considerable attention has been paid to preterm infants of greater gestational ages due to an increasing recognition that they contribute significantly to the total number of neonatal deaths. An analysis of gestational age distribution among preterm singleton infants born in 2002 shows that greater than 80% were delivered between 33 and 36 weeks of gestation.[35] In fact, most of the 33% increase in the rate of preterm births since 1981 can be attributed to the increases in late preterm infants.[36]

Late preterm infants born at 34 to 36 weeks have a mortality risk approximately 3 times that of term infants and that surviving late preterm infants are at increased risk for neonatal morbidities and cognitive problems throughout childhood.[9,10,11] Recently published studies have demonstrated that newborns born at 35 to 36 weeks of gestation experience significant mortality and morbidity, with a greater incidence of hypoglycemia, hypothermia, jaundice, and RDS compared with term infants.[37] In addition, late preterm term infants have longer hospital stays with higher associated costs, and are considerably

more likely to require rehospitalization.[11,37] Based upon these new data, it is clear that the at-risk neonatal population includes all births prior to 37 weeks, and that treatment strategies need to address both very preterm and late preterm birth.

2.1.2 Current Treatment Strategies for Preterm Birth

Prophylactic methods for prevention of preterm birth, including drugs, bed rest, or other interventions such as prophylactic cerclage, have been shown in most studies to be ineffective.[14,15] Despite widespread use, conclusive clinical evidence to support the use of prophylactic cerclage in preventing preterm birth is limited. Four randomized trials evaluating cerclage in women with historic risk factors failed to demonstrate a reduction in birth before 37 weeks gestation as well as any positive effect on neonatal outcomes.[38,39,40,41] Three other studies evaluating cerclage in preventing preterm birth in women with a demonstrated short cervix upon second trimester ultrasound have been conducted, with only 1 study demonstrating potential benefit.[42,43,44] Althuisius et al investigated the efficacy of cervical cerclage plus bed rest versus bed rest alone, and demonstrated that cervical cerclage can reduce birth before 34 weeks gestation, however, no difference between groups were observed for neonatal outcomes.[42] In summary, the evidence supporting cervical cerclage does not support its use in all populations of pregnant women; however, ongoing research may shed light on specific populations that may benefit.[45]

Available data indicate that tocolytic drugs are not effective in preventing preterm birth or in improving perinatal outcomes but may be given to reduce the frequency of uterine contractions after the onset of labor. A number of trials have evaluated the efficacy of tocolytic therapy for the prevention of preterm birth. Only 1 trial was successful in increasing the rate of term births and increasing birth weight.[46] Among the other studies, 1 trial showed an increase in the mean estimated gestational age at delivery, 2 trials prolonged delivery in terms of days, and 2 other studies did not observe any benefit.[47,48,49,50,51] While the aforementioned trials evaluated beta-mimetics versus placebo, other trials have investigated magnesium sulfate. One trial evaluating magnesium sulfate demonstrated a significant pregnancy prolongation of greater than 48 hours (acute tocolysis), although the gestational age at birth was higher in the placebo group overall.[52] A recently published meta-analysis of 9 trials comparing various tocolytic agents exhibited mixed results and concluded that maintenance therapy with tocolytics is of little to no value.[53]

One of the few preventive measures to have shown effectiveness in randomized trials is the use of progesterone agents.[16,17] Progesterone has been shown to support gestation and to inhibit uterine activity.

2.2 17 α-HYDROXYPROGESTERONE CAPROATE

2.2.1 Rationale for Use in Prevention of Preterm Birth

17 α-hydroxyprogesterone caproate (17-HPC) is a long-acting esterified derivative of the naturally occurring hormone, 17 α-hydroxyprogesterone. Like its endogenous precursor, 17-HPC has no androgenic activity. Unlike its endogenous precursor, 17-HPC has

substantial progestational activity and a prolonged duration of action.[18,19] The mechanisms by which 17P prevents preterm birth are unknown and most likely pleiotropic in nature. Putative mechanisms include a direct relaxation of the myometrium or possibly genomic effects, which may include changes in transcription of genes and differential expression of progesterone receptor isoforms.[54] Other genomic mechanisms that have been proposed include inhibition of proinflammation, which is associated with production of prostaglandins and down-regulation of estrogen receptors.[55,56,57,58,59] Lastly, a nongenomic mechanism has been hypothesized that involves inhibition of the uterotonic effects of oxytocin on the myometrium via direct interaction with the oxytocin receptor.[60]

17-HPC has a long history of use in pregnant women dating back numerous decades, including a number of published controlled studies supporting 17-HPC for prevention of preterm births.[20,21,22,23] However, the individual studies differed in the risk status of the populations studied, the use of concurrent interventions (such as cervical cerclage) and the timing and dosage of 17-HPC. A meta-analysis of data from these 17-HPC clinical trials was performed by Keirse.[16] The odds ratio for 17-HPC to reduce preterm birth was 0.5 (95% confidence interval [CI] 0.30–0.85), indicating a significant reduction in the incidence of preterm birth following 17-HPC treatment. Likewise, the odds ratio demonstrated significant reductions in preterm labor and birth weight <2500 g following 17-HPC use. Pooled odds ratios demonstrated no significant effect on rates of miscarriage, perinatal death, or neonatal complications. Although this meta-analysis confirmed the effectiveness of 17-HPC, the differences in methodology, treatment regimens, and small sample sizes in the previous studies of 17-HPC did not allow for a consensus on the appropriate use of 17-HPC to reduce preterm birth.

Recognizing these unresolved issues and the compelling need to reduce preterm birth, the NICHD MFMU Network investigated the efficacy and safety of 17P for the prevention of recurrent preterm birth in a randomized, multicenter, double-masked, placebo-controlled clinical study. The results of the NICHD study were published by Meis and colleagues in the *New England Journal of Medicine* in 2003.[1] In the same year following the publication, the American College of Obstetricians and Gynecologists Committee on Obstetric Practice recommended that progesterone supplementation be used to reduce the risk of subsequent preterm birth in women with a documented history of at least 1 prior preterm birth.[2] However, no FDA-approved formulation of 17-HPC is currently available.

2.2.2 Marketing History of 17-HPC

The FDA first approved the use of 17-HPC in 1956. The marketed product, Delalutin (E.R. Squibb & Sons, Inc.), was approved for the treatment of habitual and recurrent abortion, threatened abortion, and postpartum after pains. In 1972, the FDA approved the use of Delalutin for the indication of control and palliation of advanced adenocarcinoma of the corpus uteri.

Delalutin is no longer marketed in the US. The FDA withdrew approval for NDA 16-911 after notification by Bristol-Myers Squibb that the drug would no longer be marketed.

The FDA stated in its withdrawal notice that the product was not being withdrawn because of safety or efficacy issues.

While no FDA-approved product is currently available, surveys have shown that use of 17P is becoming more common.[61] In questionnaires completed by 522 maternal fetal medicine specialists between December 2003 and January 2004, over one-third of respondents noted that they currently prescribe progesterone for the prevention of preterm birth. Among the 198 specialists that indicated they prescribed progesterone, 74% indicated they prescribed 17P as described in the Meis publication. A more recent survey completed in 2005 shows that the percentage of specialists prescribing progesterone has increased to 67%.[62]

Currently, only pharmacies able to compound the product fill prescriptions for 17P. Compounding pharmacies play an important role by creating customized medication for an individual patient based on allergies, dose sensitivity, or an inability to take the medication in its current dosage form. However, 17P is a drug product which does not require customization for individual use and would therefore be more appropriately supplied as an FDA-approved product under FDA oversight.

There are many benefits to having an FDA-approved product. An FDA-approved product would come with standardized labeling, including information on precautions and warnings, as well as detailed instructions for administration and dosing. Additionally, FDA approval will ensure preparation of the product under Good Manufacturing Practices which will provide consistency of the quality of the final product. Additionally, an FDA-approved product is subject to regulations concerning postmarketing safety surveillance. Lastly, an FDA-approved product will allow broad scale distribution thereby increasing availability of 17P to physicians and patients who are unfamiliar with compounded products.

2.2.3 Adeza Biomedical Development of GESTIVA

Recognizing the benefit of having a 17P product manufactured under FDA requirements and subject to postmarketing safety surveillance, Adeza Biomedical (Adeza) has recently submitted a 505(b)(2) NDA to market GESTIVA (17P) as a weekly injection for the prevention of preterm birth in pregnant women with a history of at least 1 spontaneous preterm birth.

Adeza is a medical technology company with a primary focus on pregnancy-related and female reproductive disorders, including preterm birth and infertility. Adeza requested and was granted nonexclusive access to the NICHD MFMU Network data previously published by Meis et al.[1] In preparation for their NDA submission for GESTIVA, Adeza had multiple meetings with the FDA to discuss the development of the NDA and the appropriateness of the data to be submitted. As requested by the FDA, full clinical study data collected by the NICHD MFMU Network were submitted as part of the NDA as well as follow-up data on the infants born to women enrolled in the NICHD study. A discussion of the clinical studies of 17P follows in Section 3.

It is important to note that the to-be-marketed formulation of 17P is identical to the 17P product used in the NICHD clinical studies and was formulated using the same source of

active ingredient and has the same components, composition and packaging as the 17P used in the NICHD clinical studies. The 17P product is supplied as a sterile solution containing 17 α-hydroxyprogesterone caproate 25% (v/v), benzyl benzoate 46% (v/v), castor oil 28.6% (v/v), and benzyl alcohol 2% (v/v), as preservative.

3. NICHD CLINICAL STUDIES OF 17P

The NICHD conducted a multicenter, randomized, double-masked, placebo-controlled study to evaluate the use of 17 α-hydroxyprogesterone caproate injection, 250 mg/mL (17P) for the prevention of recurrent preterm birth. The study enrolled a high-risk population of pregnant women at 19 study centers. Women enrolled in the study had a current pregnancy at a gestational age of 16^0 to 20^6 weeks with a history of previous singleton spontaneous preterm delivery (SPTD). The main exclusion criteria were multifetal gestation, known major fetal anomaly or fetal demise, prior progesterone treatment or heparin therapy during current pregnancy, history of thromboembolic disease, or maternal medical/obstetrical complications (eg, current or planned cerclage, hypertension requiring medication, and seizure disorder). After 463 of the 500 proposed patients were enrolled, enrollment in this study was stopped on the recommendation of an independent Data and Safety Monitoring Committee (DSMC) when an interim analysis of 351 completed patients demonstrated a beneficial effect of 17P in reducing preterm birth $<37^0$ weeks of gestation. Those patients already enrolled in the study continued receiving study drug in a blinded fashion until the study was completed per protocol. The results from this completed study, hereafter referred to as Study 17P-CT-002, form the primary basis for the efficacy claim for 17P.

The NICHD also conducted a follow-up safety study to provide long-term follow-up data from infants born in the NICHD study. The FDA discussed with Adeza and the NICHD the required design aspects of a follow-up study, noting that long-term data would be required from a substantial number of babies (at least 35%-50% of babies in each treatment arm of the study) through at least 2 years of age. This study was not designed to assess efficacy. Rather, Study 17P-FU was designed and implemented to determine whether there is a difference in achievement of developmental milestones and physical health between children exposed *in utero* to 17P and those exposed *in utero* to placebo in Study 17P-CT-002. Women who were enrolled in Study 17P-CT-002 whose liveborn infant survived to be discharged from the hospital were contacted and asked if their child would participate in a follow-up study of the child's health status. Only patients enrolled in Study 17P-CT-002 at study sites that were active members of the MFMU Network in 2005 were considered eligible for the study. The results from Study 17P-FU are included in the safety evaluation of 17P.

Prior to conducting Study 17P-CT-002, the NICHD had initiated an earlier study with the same protocol design, inclusion and exclusion criteria, and study procedures but with a different manufacturer of study drug (Study 17P-IF-001). The study was terminated after only one-third of the proposed patients were enrolled because the study drug (17P) was recalled by the manufacturer due to violations of manufacturing practices. The recall was applicable to all products manufactured by the plant and was not limited to 17P. The study drug used in the terminated study is referred to as the Initial Formulation (IF). Because only 104 of a planned 500 patients were not withdrawn from Study 17P-IF-001 due to termination of the study, the efficacy data from the terminated study are not considered adequate to allow for any meaningful interpretation of differences in preterm birth rates between 17P and placebo. However, rather than dismissing these data, data

from this terminated study were combined with the data from Study 17P-CT-002 to further explore the efficacy and safety of 17P.

The primary assessment of efficacy presented in the 505(b)(2) submission and in this document focuses on the completed Study 17P-CT-002. While the efficacy data from the terminated study were not considered meaningful on their own, the 17P-IF-001 data were combined with the 17P-CT-002 data for analyses to further assess the efficacy of 17P. In evaluating the clinical safety of 17P in pregnant women, data from both Study 17P-IF-001 and Study 17P-CT-002 were integrated into 1 database, compiling safety data from the 2 studies. Long-term follow-up data on the health and development of infants born during the 17P-CT-002 study collected in the noninterventional 17P-FU study are also included in the overall safety assessment.

Table 3-1 presents a summary of the clinical studies summarized in the efficacy and safety evaluation of 17P for the prevention of preterm birth.

Table 3-1. NICHD Clinical Studies of 17P

Protocol #; Status	Study Design	Study Population	Treatment Dose	Duration of Drug Treatment	Number of Patients	Mean Age (Range)
17P-CT-002; Completed [a] Aug 2002	Double-masked, placebo-controlled, randomized 2:1 17P to placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation through 36^6 wks gestation or birth[b]	463 17P: 310 Placebo: 153	26.2 yr (16, 43)
Study 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	278 17P: 194 Placebo: 84	47.4 mo (30, 64)
17P-IF-001; Terminated [c] Feb 1999	Double-masked, placebo-controlled, randomized 2:1 17P to placebo	Pregnant women with previous spontaneous preterm birth	250 mg/week	Weekly injections beginning from 16^0 to 20^6 wks gestation through 36^6 wks gestation or birth[b]	150 17P: 94 Placebo: 56	26.2 yr (17, 42)

[a] An independent DSMC reviewed study data after 400 patients had completed the study. Based on that interim data set, the DSMC recommended that enrollment be discontinued because 17P had shown significant benefit for the primary outcome (preterm birth $<37^0$ weeks). At the time the DSMC made its recommendation to stop enrollment, 463 patients had been enrolled, which was 93% of the proposed sample size of 500 patients.

[b] Gestational age is reported in weeks with days in superscript. For example, a gestational age of 36 weeks 6 days is presented as 36^6, and 37 weeks 0 days is presented as 37^0.

[c] Study 17P-IF-001 was terminated early by NICHD when the manufacturer recalled the study drug. The last patient visit was in August 1999. Only 104 patients (65 in the 17P group and 39 in the placebo group) were not withdrawn from the study due to study termination.

4. EFFICACY EVALUATION

4.1 EFFICACY OF 17P IN NICHD CLINICAL STUDIES

4.1.1 Patient Disposition

The disposition of patients in Study 17P-CT-002 is summarized in Figure 4-1. A total of 463 patients were enrolled and randomized to treatment; 310 in the 17P group and 153 in the placebo group. A comparable percentage of patients in each treatment group completed injections through 36^{6} weeks gestation or birth, whichever occurred first. Early withdrawal from study drug occurred at a similar rate in both treatment groups. Most of these patients discontinued due to nonclinical reasons, which were not further defined. Four patients, all in the 17P group, were lost to follow-up.

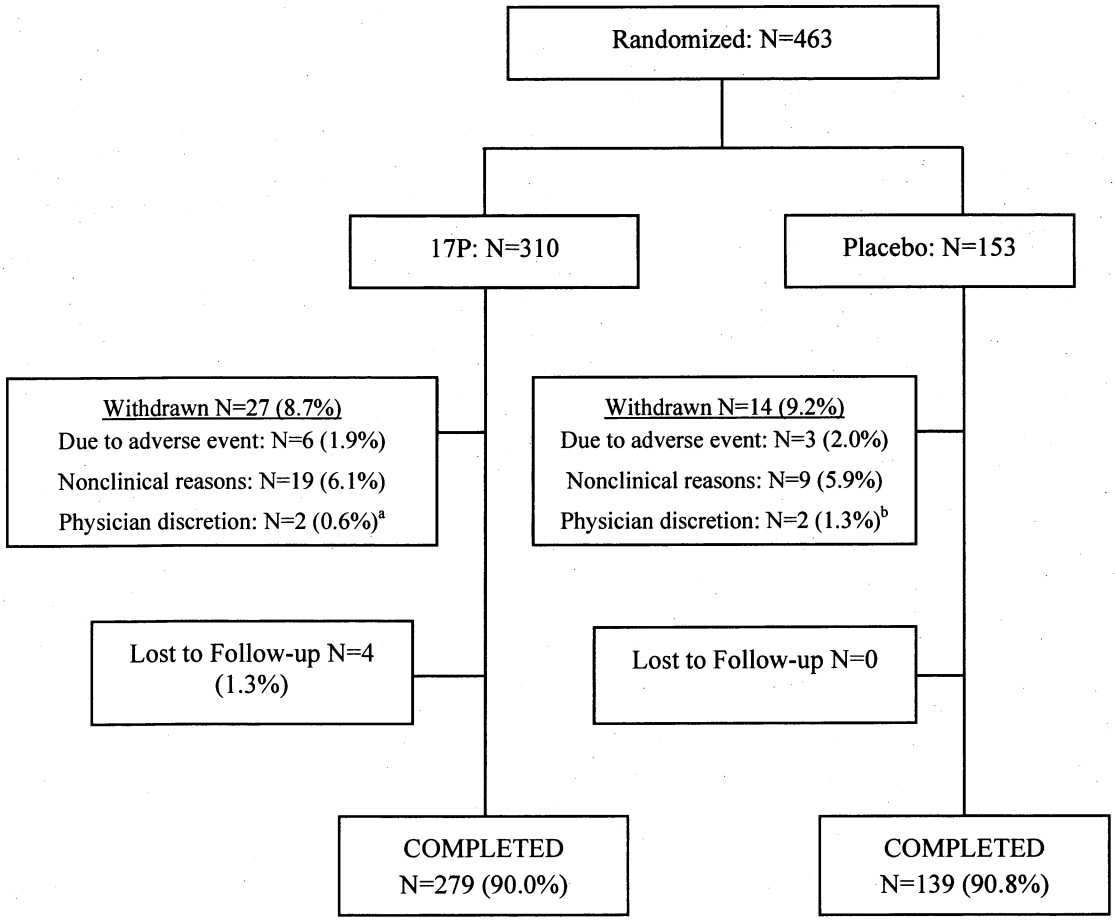


Figure 4-1. Patient Disposition

Note: "Withdrawn from the study" was defined as the patient no longer received study drug. "Lost to follow-up" was defined as the patient's delivery data could not be obtained.

[a] In the 17P group, an investigator stopped the participation of one patient due to injection site reactions. Therefore, 7 (2.2%) patients in the 17P group discontinued due to AEs.

[b] In the placebo group, an investigator stopped the participation of 1 patient due to a potential allergic reaction. Therefore, 4 (2.6%) patients in the placebo group discontinued due to AEs.

4.1.2 Patient Demographics and Baseline Characteristics

The baseline characteristics of patients enrolled in Study 17P-CT-002 were comparable between treatment groups (Table 4-1). More than half of the patients were African American (59%). The age of the patients ranged from 16 to 43 years.

Table 4-1. Demographics and Baseline Characteristics

Characteristic	17P N=310	Placebo N=153	*P* value
Age, yr			0.2481[d]
Mean (SD)	26.0 (5.6)	26.5 (5.4)	
Min, Max	16, 43	16, 40	
Race or ethnic group, n (%)[a]			0.8736[b]
African American	183 (59.0)	90 (58.8)	
Caucasian	79 (25.5)	34 (22.2)	
Hispanic	43 (13.9)	26 (17.0)	
Asian	2 (0.6)	1 (0.7)	
Other	3 (1.0)	2 (1.3)	
Marital status, n (%)			0.6076[b]
Married or living with partner	159 (51.3)	71 (46.4)	
Divorced, widowed, or separated	32 (10.3)	18 (11.8)	
Never married	119 (38.4)	64 (41.8)	
Prepregnancy BMI (kg/m^2)			0.3310[d]
Mean (SD)	26.9 (7.9)	26.0 (7.0)	
Min, Max	15.2, 72.2	16.1, 50.7	
Years of education			0.2175[d]
Mean (SD)	11.7 (2.3)	11.9 (2.3)	
Min, Max	2, 16	3, 16	
Diabetes, n (%)	13 (4.2)	4 (2.6)	0.3954[b]
Smoked cigarettes during pregnancy, n (%)	70 (22.6)	30 (19.6)	0.4647[b]
Alcoholic drinks during pregnancy, n (%)	27 (8.7)	10 (6.5)	0.4172[b]
Used street drugs during pregnancy, n (%)	11 (3.5)	4 (2.6)	0.7822[c]

Abbreviations: body mass index (BMI)

[a] Race or ethnic group was self-assigned by the women.

[b] *P* value from the chi-square test.

[c] *P* value from the Fisher exact test.

[d] *P* value from the Wilcoxon rank sum test.

Obstetrical histories of patients enrolled in Study 17P-CT-002 were comparable with the exception of statistically significant (P=0.0068) difference in the number of previous preterm deliveries (Table 4-2). Likewise, the percentage of patients who had >1 previous preterm birth was significantly (P=0.0036) lower in the 17P group (28%) compared with the placebo group (41%). Adjustments were made to the analysis of the primary endpoint

(preterm birth <37^0 weeks gestation) that demonstrated that this imbalance did not impact the efficacy results of the study.

Table 4-2. Previous and Current Obstetrical History

Obstetrical History	17P N=310	Placebo N=153	*P* value
No. of previous preterm deliveries			0.0068[c]
Mean (SD)	1.4 (0.7)	1.6 (0.9)	
Min, Max	1, 5	1, 6	
>1 Previous preterm birth, n (%)	86 (27.7)	63 (41.2)	0.0036[a]
No. of previous SPTD			0.0017[c]
Mean (SD)	1.3 (0.7)	1.5 (0.9)	
Min, Max	1, 5	1, 6	
No. of previous term deliveries			0.6650[c]
Mean (SD)	0.8 (1.1)	0.7 (1.0)	
Min, Max	0, 7	0, 5	
Duration of gestation at randomization, wk			0.5929[c]
Mean (SD)	18.9 (1.4)	18.8 (1.5)	
Min, Max	16, 21	16, 21	
Gestational age of qualifying delivery, wk			0.2078[c]
Mean (SD)	30.6 (4.6)	31.3 (4.2)	
Min, Max	20, 36	20, 36	
Previous miscarriage, n (%)	93 (30.0)	57 (37.3)	0.1166[a]
Previous stillbirth, n (%)	31 (10.0)	13 (8.5)	0.6039[a]
Infection during pregnancy (before randomization), n (%)	98 (31.6)	55 (35.9)	0.3510[a]
Corticosteroids during pregnancy (before randomization), n (%)	5 (1.6)	8 (5.2)	0.0359[b]

Abbreviations: spontaneous preterm delivery (SPTD)

[a] *P* value from the chi-square test.

[b] *P* value from the Fisher exact test.

[c] *P* value from the Wilcoxon rank sum test.

4.1.3 Efficacy Results

4.1.3.1 Prevention of Preterm Birth <37^0 Weeks

The primary efficacy outcome was preterm birth <37^0 weeks (as determined by project gestational age). All deliveries occurring from randomization through 36^6 weeks gestation, including any miscarriages and elective abortions, were to be counted in the primary outcome.

Treatment with 17P was effective in reducing preterm birth prior to 37^0 weeks of gestation as shown in Table 4-3. The incidence of deliveries prior to 37^0 weeks gestation was significantly lower in the 17P group than the placebo group whether examined using the intent-to-treat (ITT) population (*P*=0.0003) or all-available-data population, which excluded the 4 patients lost to follow-up. The incidence of preterm birth was reduced

32% following 17P treatment compared with placebo in the ITT population, yielding a relative risk for preterm birth of 0.68 (95% CI: 0.55 – 0.83) for 17P. The incidence of preterm birth was reduced 34% following 17P treatment compared with placebo in the all-available-data population.

The effect of 17P was apparent even after adjusting for the imbalance in the number of preterm deliveries. The adjusted incidence of deliveries prior to 37^0 weeks gestation remained significantly lower among the 17P group (P=0.0010) indicating that the baseline imbalance was not driving the differences between the 17P and placebo groups.

Table 4-3. Preterm Birth <37^0 Weeks

	17P		Placebo		
Data Source	**N**	**n (%)**	**N**	**n (%)**	***P* value**
ITT population (all data)	310	115 (37.1)	153	84 (54.9)	0.0003[a] 0.0010[b]
All available data	306	111 (36.3)	153	84 (54.9)	0.0001[a] 0.0006[b]

Note: ITT population was all randomized patients. Patients with missing outcome data were classified as having a preterm birth <37^0 weeks (treatment failure). All-available-data population excludes 4 patients lost to follow-up and is synonymous with that presented by Meis et al.[1]

[a] *P* value from chi-square test.

[b] *P* value from a logistic regression adjusting for the number of previous preterm deliveries.

As with the overall rate of deliveries <37^0 weeks, the incidence of SPTD <37^0 weeks gestation was significantly lower in the 17P group compared with the placebo group (P=0.0017). This difference was primarily due to the rate of spontaneous births <37^0 weeks gestation with preterm labor (P=0.0026).

Table 4-4. Spontaneous Preterm Delivery <37^0 Weeks

Pregnancy Outcome	**17P N=310 n (%)**	**Placebo N=153 n (%)**	***P* value[b]**
Spontaneous delivery[a] <37^0	94 (30.3)	69 (45.1)	0.0017
SPTD <37^0 due to pPROM	26 (8.4)	16 (10.5)	0.4656
SPTD <37^0 due to preterm labor	67 (21.6)	53 (34.6)	0.0026
SPTD <37^0 due to preterm labor or pPROM	89 (28.7)	69 (45.1)	0.0005
Indicated delivery <37^0	25 (8.1)	15 (9.8)	0.5309

Abbreviations: preterm premature rupture of membranes (pPROM)

Note: Data presented are from the ITT analysis. The ITT population was all randomized patients. Patients with missing outcome data were classified as having a preterm birth <37^0 weeks (treatment failure).

[a] Spontaneous delivery includes delivery following preterm labor or pPROM and miscarriages <20 weeks gestation.

[b] *P* value from chi-square test.

4.1.3.2 Prevention of Preterm Birth <37^0 Weeks in Subsets of the Overall Population

Treatment with 17P was effective in reducing preterm birth prior to 37^0 weeks gestation irrespective of the gestational age of the qualifying delivery, race, or number of previous preterm births (Table 4-5). Subgroup analyses were performed after stratifying patients by number of previous preterm deliveries (1, 2, ≥3), by gestational age of the previous qualifying SPTD (20^0-<28^{0}weeks, 28^0-<32^0 weeks, 32^0-<35^0 weeks, 35^0-<37^0 weeks), and by race (African American, non-African American). A Breslow-Day test demonstrated that the treatment effect of 17P was consistent across strata as indicated by nonsignificant *P* values. These results are particularly important as prior preterm deliveries, gestational age of a previous preterm birth, and African American race are all risk factors for preterm birth.[5,6,30,63]

Table 4-5. Preterm Birth <37^0 Weeks by Number of Previous Preterm Deliveries, Gestational Age of Qualifying Delivery, and Race

Characteristic	17P n/N[a] (%)	Placebo n/N[a] (%)	*P* value[b]
Number of previous preterm births (PTBs)			0.4681
1 prior PTB	74/224 (33.0)	40/90 (44.4)	
>1 prior PTB	41/86 (47.7)	44/63 (69.8)	
2 prior PTB	27/56 (48.2)	31/46 (67.4)	
≥3 prior PTB	14/30 (46.7)	13/17 (76.5)	
Previous SPTD (qualifying delivery) by gestational age			0.7261
20^0 - <28^{0}weeks	33/82 (40.2)	19/29 (65.5)	
28^0 - <32^0 weeks	21/66 (31.8)	17/30 (56.7)	
32^0 - <35^0 weeks	30/84 (35.7)	27/55 (49.1)	
35^0 - <37^0 weeks	31/78 (39.7)	21/39 (53.8)	
Race			0.7021
African American	66/183 (36.1)	47/90 (52.2)	
Non-African American	49/127 (38.6)	37/63 (58.7)	

Abbreviation: spontaneous preterm delivery (SPTD), preterm birth (PTB).

Note: Data based on ITT population (all randomized patients). Patients with missing outcome data were classified as having a preterm birth <37^0 weeks (treatment failure).

[a] n represents the number of patients in a specific category who delivered <37^0 weeks gestation; N represents the number of patients overall in a specific category.

[b] *P* value from the Breslow-Day test for consistency of response across categories.

4.1.3.2.1 Number of Previous Preterm Births

Treatment with 17P reduced the rate of preterm births <37^0 weeks gestation regardless of whether the patient had 1, 2 or ≥3 previous preterm births (Table 4-5). In both treatment groups, patients who had more than 1 previous preterm birth had higher rates of preterm

birth <37^0 week gestation than patients who had only one previous preterm birth. The incidence of preterm birth <37^0 weeks was reduced by 26% compared with placebo following 17P treatment among women with 1 previous preterm birth (from 44.4% in the placebo group to 33% in the 17P group) and was reduced by 32% compared with placebo following treatment with 17P among women with >1 previous preterm birth (from 69.8% in the placebo group to 47.7% in the 17P group).

4.1.3.2.2 Gestational Age of Qualifying Delivery

Treatment with 17P reduced the rate of preterm birth <37^0 weeks in all 4 gestational age categories (Figure 4-2). Following treatment with 17P, the incidence of preterm birth was reduced by 39% compared with placebo for women with a qualifying prior preterm birth between 20^0 and <28^0 weeks gestation (from 65.5% in the placebo group to 40.2% in the 17P group). The incidence of preterm birth following treatment with 17P was reduced by 44% compared with placebo for women who had a qualifying prior preterm birth between 28^0 and <32^0 weeks gestation (from 56.7% in the placebo group to 31.8% in the 17P group). The incidence of preterm birth following treatment with 17P was reduced by 27% compared with placebo for women who had a qualifying prior preterm birth between 32^0 and <35^0 weeks gestation (from 49.1% in the placebo group to 35.7% in the 17P group). And finally, the incidence of preterm birth following treatment with 17P was reduced by 26% compared with placebo for women who had a qualifying prior preterm birth between 35^0 and <37^0 weeks gestation (from 53.8% in the placebo group to 39.7% in the 17P group).

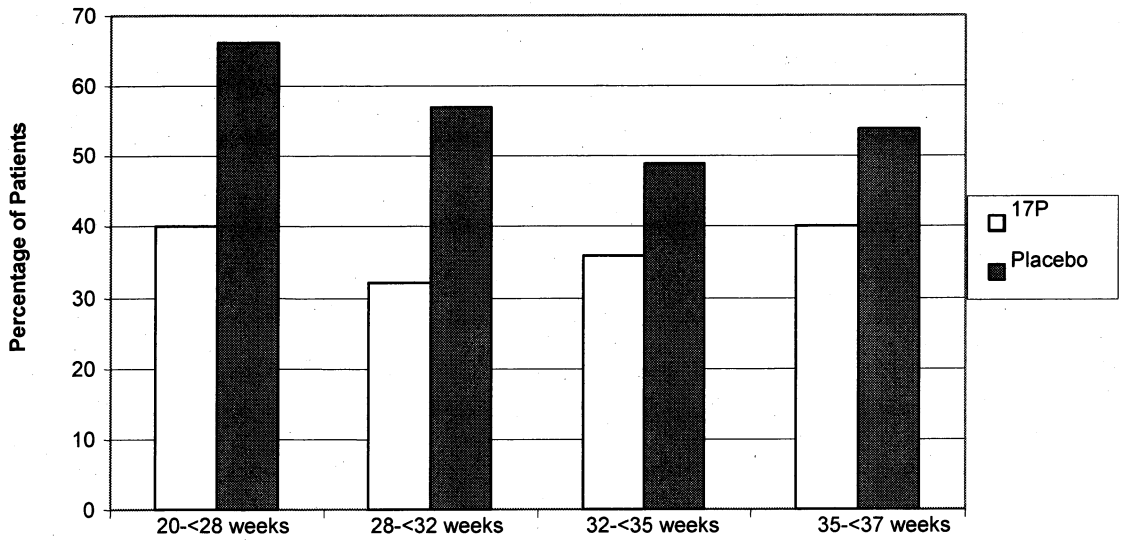


Figure 4-2. Preterm Birth <37^0 Weeks by Gestational Age of Qualifying Delivery and Treatment

4.1.3.2.3 Race (African American versus Non-African American)

Treatment with 17P reduced the rate of preterm birth <37^0 weeks gestation in both African American and non-African American women (Figure 4-3). Following treatment with 17P, the incidence of preterm birth <37^0 weeks was reduced by 31% compared with placebo among African American women (from 52.2% in the placebo group to 36.1% in the 17P group) and by 34% compared with placebo among non-African American women (from 58.7% in the placebo group to 38.6% in the 17P group).

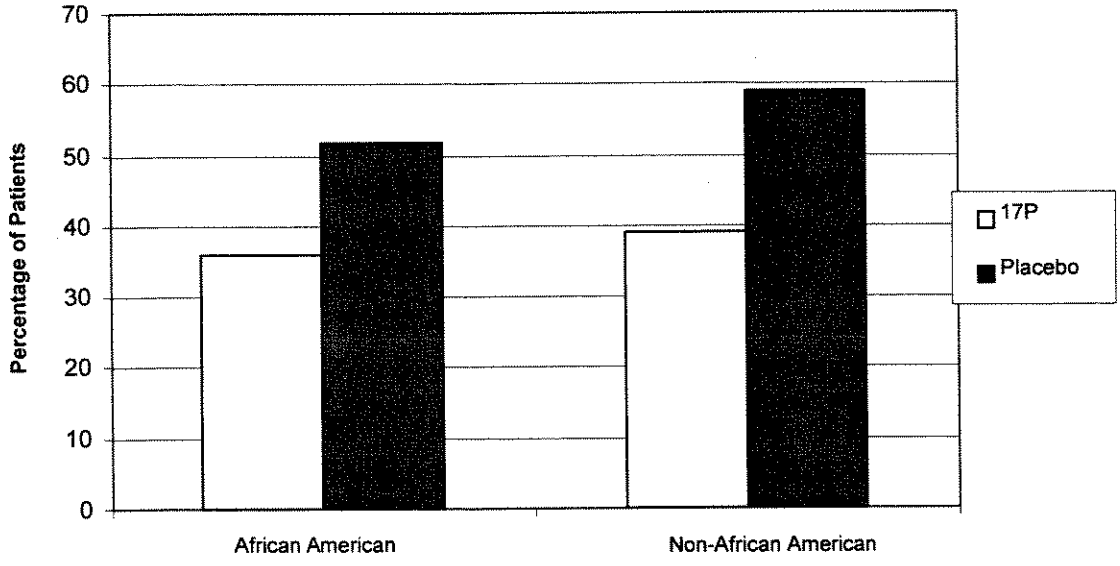


Figure 4-3. Preterm Birth <37^0 Weeks by Race and Treatment

4.1.3.3 Prevention of Preterm Birth <35^0, <32^0, and <30^0 Weeks

Treatment with 17P was effective in reducing preterm birth whether preterm was defined as <37^0, <35^0, <32^0, or <30^0 weeks gestation. As shown in Table 4-6, rates of deliveries <35^0 weeks gestation (P=0.0324), <32^0 weeks gestation (P=0.0458), and <30^0 weeks gestation (P=0.0329) were all significantly lower in the 17P group compared with the placebo group.

Table 4-6. Secondary Pregnancy Outcomes

Pregnancy Outcome	17P N=310 n (%)	Placebo N=153 n (%)	Relative Risk (95% CI)	*P* value[a]
Preterm Birth <35^0	67 (21.6)	47 (30.7)	0.70 (0.51 – 0.97)	0.0324
Preterm Birth <32^0	39 (12.6)	30 (19.6)	0.64 (0.42 – 0.99)	0.0458
Preterm Birth <30^0	28 (9.0)	24 (15.7)	0.58 (0.35 – 0.96)	0.0329
Preterm Birth <28^0	27 (8.7)	16 (10.5)	0.83 (0.46 – 1.50)	0.5422
Preterm Birth <24^0	15 (4.8)	5 (3.3)	1.48 (0.55 – 4.00)	0.4342

Abbreviations: confidence interval (CI)

Note: Data presented are from the ITT analysis. The ITT population was all randomized patients. Patients with missing outcome data were classified as having a preterm birth <37^0 weeks (treatment failure).

[a] *P* value from chi-square test.

Figure 4-4 illustrates the effectiveness of 17P in reducing preterm birth irrespective of the definition applied. Following treatment with 17P, the incidence of preterm birth was reduced by approximately 42%, 36%, 30%, and 32% and when defined as <30^0, <32^0, <35^0, and <37^0 weeks, respectively.

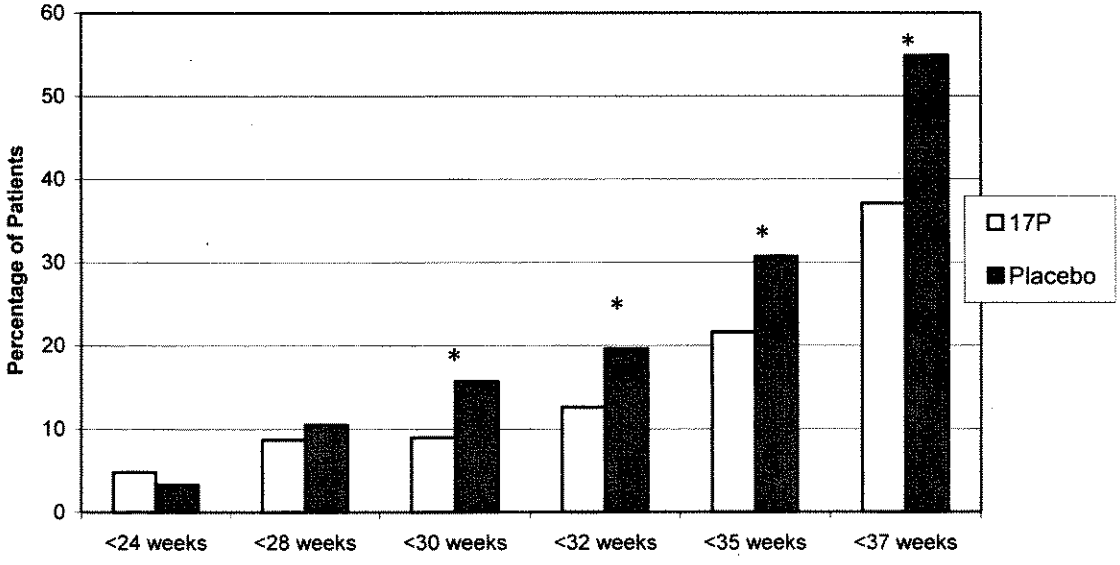


Figure 4-4. Preterm Birth <37^0, <35^0, <32^0, <30^0, <28^0, and <24^0 Weeks

*Statistically significant difference; *P* <0.05.

4.1.3.4 Prolongation of Pregnancy

Treatment with 17P significantly prolonged pregnancy when compared with placebo. Treatment with 17P prolonged gestation (from the time of randomization) from a mean of 125 days for women who received placebo to 131 days for women who received 17P (P=0.0024). Accordingly, the mean gestational age at the time of birth was 1 week higher in the 17P group (36.2 weeks) compared with placebo (35.2 weeks; P=0.0024).

Treatment with 17P also resulted in a distinct shift in the distribution of gestational ages at birth. As shown in Table 4-7, the percentage of infants born at term (>37^0 weeks) was markedly higher in the 17P group (62.9%) compared with the placebo group (45.1%). In contrast, the percentage of infants born at all gestational ages less than 32 weeks was nearly half in the 17P group (11.9%) compared with the placebo group (19.6%). This shift in distribution illustrates the effectiveness of 17P in preventing preterm birth and prolonging pregnancy.

Table 4-7. Distribution of Gestational Ages at Birth

Gestational Age at Birth	17P N=310 n (%)	Placebo N=153 n (%)
>37^0 weeks (term births)	195 (62.9)	69 (45.1)
35^0-<37^0 weeks	49 (15.8)	37 (24.2)
32^0-<35^0 weeks	29 (9.4)	17 (11.1)
28^0-<32^0 weeks	8 (2.6)	14 (9.2)
24^0-<28^0 weeks	12 (3.9)	11 (7.2)
20^0-<24^0 weeks	11 (3.5)	5 (3.3)
16^0-<20^0 weeks	6 (1.9)[a]	0 (0)

Note: Data from 4 patients lost to follow-up are included in this analysis. These patients are considered to have delivered at the gestational age interval when they were lost to follow-up.

[a] Includes miscarriages <20^0 weeks.

The ability of 17P treatment to prolong pregnancy is further demonstrated by the hazard ratios for delivery at each gestational age time interval. The hazard ratio is the probability that a 17P patient who has not delivered at the start of a gestational age interval will deliver in that interval compared with a placebo patient. As shown in Table 4-8, a woman treated with 17P is less likely to give birth at each gestational age interval from 24 weeks of gestation up to 37 weeks of gestation than a woman receiving placebo.

Table 4-8. Hazard Ratio for Delivery – 17P Relative to Placebo

Gestational Age	Hazard Ratio (95% CI)
$>37^0$ weeks (term births)	ND
35^0-$<37^0$ weeks	0.52 (0.28 – 0.94)
32^0-$<35^0$ weeks	0.73 (0.31 – 1.70)
28^0-$<32^0$ weeks	0.27 (0.08 – 0.90)
24^0-$<28^0$ weeks	0.54 (0.17 – 1.72)
20^0-$<24^0$ weeks	1.01 (0.23 – 4.50)
16^0-$<20^0$ weeks	ND

Abbreviations: not determined (ND).

Note: The hazard ratio for the interval from 16^0-$<20^0$ weeks could not de determined since the hazard function in the placebo group is 0. The hazard ratio for $>37^0$ weeks (term births) is 1 because all patients eventually deliver. Therefore, no standard error can be calculated and no confidence interval can be constructed.

4.1.3.5 Neonatal Outcomes

Treatment with 17P significantly reduced the number of low birth weight infants. As shown in Table 4-9, the percentage of infants weighing <2500 g was significantly (P=0.0029) lower in the 17P group (27.2%) than in the placebo group (41.1%). Treatment with 17P also reduced the incidence of infants weighing <1500 g, but the difference did not reach statistical significance (P=0.0834).

Treatment with 17P also resulted in fewer admissions to the NICU. A significantly smaller percentage of live infants in the 17P group were admitted to the NICU compared with live infants in the placebo group (P=0.0434) (Table 4-9). Also, the median time spent in the NICU was shorter for the 17P group than the placebo group, but the difference was not statistically significant (P=0.1283). Likewise, the overall mean days in the hospital among all infants was lower in the 17P group compared with the placebo group, but the difference was not statistically significant (P=0.3612).

There were no differences between treatment groups in mean birth weight, head circumference, scores reflecting condition of newborn (Apgar scores), or the appearance of congenital anomalies. Congenital anomalies identified at birth are discussed in more detail in Section 5.1.3.3.2.

Table 4-9. Neonatal Outcomes

Neonatal Outcome	17P	Placebo	*P* value
Birth weight (g)	N=301	N=151	--
Mean (SD)	2760 (859)	2582 (942)	0.0736[c]
Min, Max	208, 4900	300, 4855	--
Birth weight <2500 g, n (%)	82 (27.2)	62 (41.1)	0.0029[a]
Birth weight <1500 g, n (%)	26 (8.6)	21 (13.9)	0.0834[a]
Congenital anomalies, n (%)	N=302	N=153	--
	6 (2.0)	3 (2.0)	1.0000[b]
Admitted to NICU or miscarriage/stillbirth/neonatal death, n (%)	N=306	N=153	--
	93 (30.4)	57 (37.3)	0.1395[a]
Admitted to NICU (live births), n (%)	N=295	N=151	--
	82 (27.8)	55 (36.4)	0.0434[c]
Days in NICU[d]	N=76	N=52	--
Median	9.1	14.1	0.1283[c]
Min, Max	0.1, 194.8	0.1, 147.0	--
Infant hospital days[e]	N=285	N=140	--
Mean (SD)	8.7 (16.0)	13.3 (26.5)	0.3612[c]
Min, Max	2, 123	2, 148	--

Abbreviations: neonatal intensive care unit (NICU)

Note: Birth weight data were missing for some infants.

[a] *P* value from the chi-square test.

[b] *P* value from the Fisher exact test.

[c] *P* value from the Wilcoxon rank sum test.

[d] For neonatal deaths, days in the NICU were calculated until date of death. However, it was set to the maximum value for the determination of the *P* value. Days in NICU could not be determined for 3 patients in the 17P group and 2 patients in the placebo group.

[e] Determined only for infants who did not die during the study.

4.1.3.6 Neonatal Morbidity and Mortality

Maternal treatment with 17P was effective in reducing serious neonatal morbidities associated with preterm birth. As shown in Table 4-10, the incidence rates of any type of IVH (*P*=0.0258) and of NEC (*P*=0.0127) were significantly lower in the 17P group compared with placebo. Likewise, the use of supplemental oxygen (*P*=0.0248) and the mean number of days of respiratory therapy were also significantly lower following 17P treatment (*P*=0.0438). The rates of bronchopulmonary dysplasia, PDA, other intracranial hemorrhages, and confirmed pneumonia were lower following 17P treatment, but the differences did not reach statistical significance.

A composite neonatal morbidity index was determined as a post hoc analysis. While there is no universal standard for defining a composite morbidity index, this assessment was based on the number of neonates who died or experienced respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 IVH, proven sepsis, or NEC. The composite

morbidity was lower in the 17P group, however, the difference was not statistically significant (*P*=0.1194).

Neonatal mortality was lower following treatment with 17P, but the difference between treatment groups was not statistically significant (*P*=0.1159). Overall fetal and neonatal mortality is discussed in detail in the safety discussion in Section 5.1.3.3.

Table 4-10. Neonatal Morbidity and Mortality for Live Births

Morbidity	17P N=295 n (%)	Placebo N=151 n (%)	*P* value
Transient tachypnea	11 (3.7)	11 (7.3)	0.0990[a]
Respiratory distress syndrome (RDS)	29 (9.9)	23 (15.3)	0.0900[a]
Bronchopulmonary dysplasia (BPD)	4 (1.4)	5 (3.3)	0.1730[b]
Persistent pulmonary hypertension	2 (0.7)	1 (0.7)	1.0000[b]
Ventilator support	26 (8.9)	22 (14.8)	0.0616[a]
Supplemental oxygen	45 (15.4)	36 (24.2)	0.0248[b]
Patent ductus arteriosus	7 (2.4)	8 (5.4)	0.1004[a]
Seizures	3 (1.0)	0	0.5541[b]
Any intraventricular hemorrhage (IVH)	4 (1.4)	8 (5.3)	0.0258[b]
Grade 3 or 4 IVH	2 (0.7)	0	0.5511[b]
Other intracranial hemorrhage	1 (0.3)	2 (1.3)	0.2628[b]
Retinopathy of prematurity	5 (1.7)	5 (3.3)	0.3164[b]
Proven newborn sepsis	9 (3.1)	4 (2.6)	1.0000[b]
Confirmed pneumonia	3 (1.0)	4 (2.7)	0.2330[b]
Necrotizing enterocolitis (NEC)	0	4 (2.7)	0.0127[b]
Composite Neonatal Morbidity Index[c]	35 (11.9)	26 (17.2)	0.1194[a]
Neonatal mortality	8 (2.7)	9 (6.0)	0.1159[b]

[a] *P* value is from the chi-square test.

[b] *P* value is from the Fisher exact test.

[c] The composite neonatal morbidity measure counted any liveborn infant who experienced 1 or more of the following: death, RDS, BPD, grade 3 or 4 IVH, proven sepsis, or NEC.

4.1.3.7 Integrated Analysis

To further explore the efficacy of 17P, the primary efficacy data collected from patients enrolled in the terminated study (Study 17P-IF-001) were combined with the primary efficacy data from Study 17P-CT-002. Analyses of integrated data from the 17P-IF-001 and 17P-CT-002 studies demonstrated the same reduction in preterm birth following 17P treatment as was observed with Study 17P-CT-002 data alone. The integrated analysis was based on a combined ITT population and included data from all patients in Study 17P-IF-001 whether or not they completed treatment.

The incidence rates of deliveries <37^0 weeks gestation, <35^0 weeks gestation, and <32^0 weeks gestation were all significantly lower in the 17P patients than in the placebo patients (Figure 4-5). The risk of giving birth <32^0, <35^0, and <37^0 weeks gestation were reduced by 32% (from 19.1% in the placebo group to 12.9% in the 17P group), 27% (from 30.6% in the placebo group to 22.3% in the 17P group), and 23% (from 49.8% in the placebo group to 38.1% in the 17P group), respectively, following treatment with 17P.

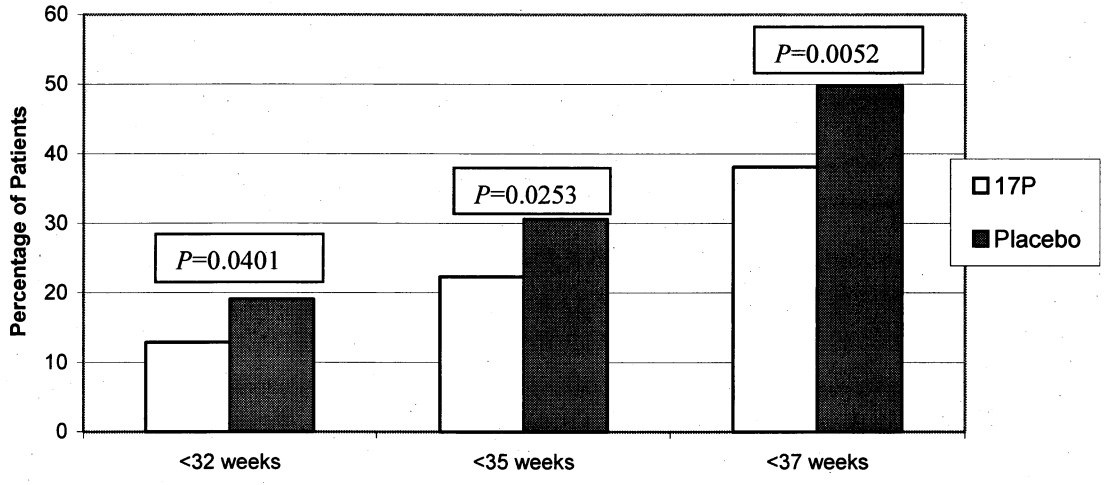
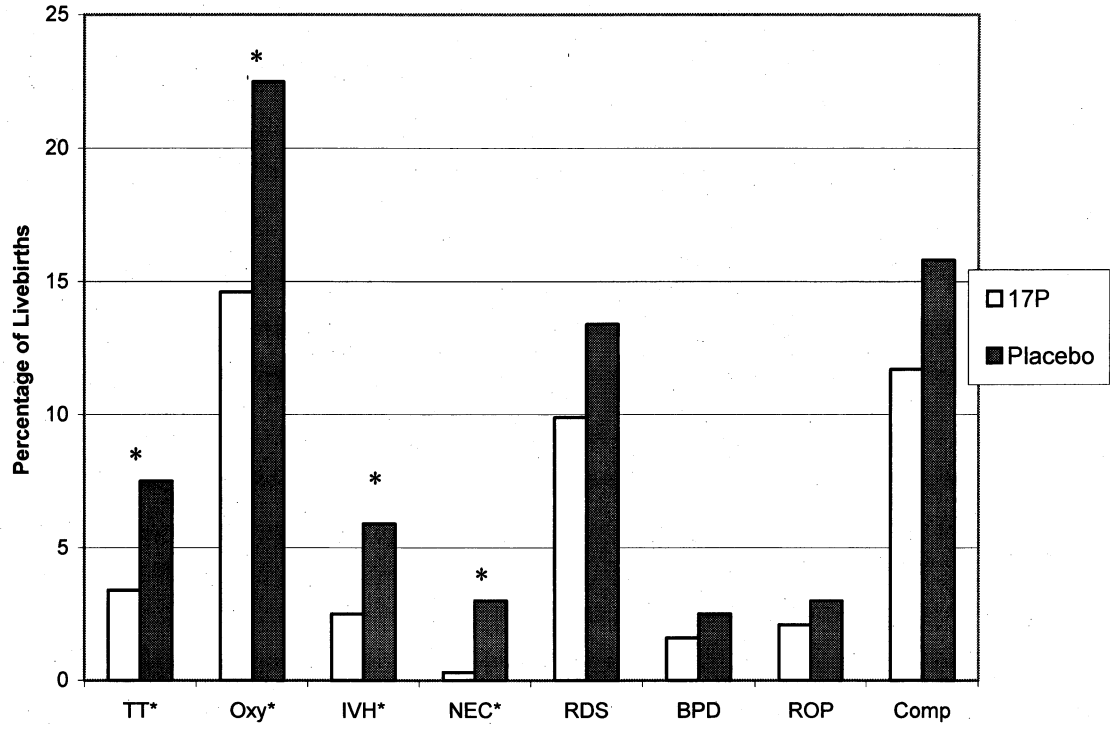


Figure 4-5. Integrated Analysis of Preterm Births <37^0, <35^0, and <32^0 Weeks

As with the data from the completed study alone, data from the integrated analysis demonstrate that 17P treatment decreased the occurrence of neonatal morbidities. As shown in Figure 4-6, treatment with 17P significantly reduced the incidence rates of transient tachypnea (from 7.5% in the placebo group to 3.4% in the 17P group), supplemental oxygen (from 22.5% in the placebo group to 14.6% in the 17P group), any type of IVH (from 5.9% in the placebo group to 2.3% in the 17P group), and NEC (from 3.0% in the placebo group to 0.3% in the 17P group). There were also nonstatistically significant reductions in RDS, BPD, ROP, and ventilator support.



Abbreviations: transient tachypnea (TT); supplemental oxygen (Oxy); intraventricular hemorrhage (IVH); necrotizing colitis (NEC); respiratory distress syndrome (RDS); bronchopulmonary dysplasia (BPD); retinopathy of prematurity (ROP); composite neonatal morbidity measure (Comp).

Figure 4-6. Integrated Analysis of Neonatal Morbidity

*Statistically significant difference; P <0.05.

4.1.4 Efficacy Conclusions from NICHD Studies

The efficacy results from the completed NICHD Study 17P-CT-002 demonstrate that treatment with 17P significantly reduces:

- preterm birth whether defined as $<37^0$ (P=0.0003), $<35^0$ (P=0.0324), $<32^0$ (P=0.0458), or $<30^0$ (0.0329) weeks gestation. Pregnancy was significantly prolonged by 17P treatment (P=0.0024) and the mean gestational age at birth was one week higher following treatment with 17P.
- preterm birth $<37^0$ weeks regardless of the gestational age of the qualifying prior preterm delivery, race (African American and non-African American), or the number of previous preterm deliveries.
- the incidence of low birth weight infants. Maternal treatment with 17P resulted in a significant reduction in the incidence of infants weighing <2500 g at birth (27.2% for 17P compared with 41.1% for placebo; P=0.0029) and a nonstatistically significant reduction in the percentage of infants weighing <1500 g (8.6% for 17P compared with 13.9% for placebo; P=0.0834).

- the incidence of live born infants admitted to the NICU (P=0.0434).
- the occurrence of serious neonatal morbidities such as NEC (P=0.0127) and any grade of IVH (P=0.0258). Maternal treatment with 17P also resulted in a significant reduction in the need for supplemental oxygen (P=0.0248) and the number of days of respiratory therapy (P=0.0438) in neonates.

In summary, the results of Study 17P-CT-002 indicate that 17P, administered as weekly intramuscular injections, when initiated from 16^0 to 20^6 weeks gestation and continued through 36^6 weeks gestation or birth, significantly reduces the risk of preterm birth and neonatal morbidities in the high-risk population of women with a prior preterm birth.

4.2 EFFICACY OF 17-HPC IN SCIENTIFIC LITERATURE

4.2.1 Controlled Clinical Studies of 17-HPC in Singleton Pregnancies

The NICHD clinical study results reinforce the positive findings from a number of smaller studies of 17-HPC. Prior to the publication of data from the completed NICHD study by Meis and colleagues, 6 controlled clinical trials had been previously published on the efficacy of 17-HPC for the prevention of preterm birth with singleton pregnancies.[20,21,22,23,24,25] These studies differed in the risk status of patients, the use of other interventions, and the timing and dosage of 17-HPC. Table 4-11 provides a summary of the incidence of preterm births reported in the previous controlled clinical trials of 17-HPC.

Table 4-11. Summary of Incidence Rates of Preterm Birth in Women with Single Gestation – Literature Review

Study	Gestation Week 17-HPC Treatment Initiated	17-HPC Rate of Preterm Birth		Placebo Rate of Preterm Birth		Odds Ratio (95% CI)
		N	n (%)	N	n (%)	
Controlled Studies in US						
LeVine 1964[20]	≤16	15	2 (13)	15	3 (20)	0.63 (0.10-4.15)[a]
Johnson 1975[22]	<24	18	2 (11)	25	12 (48)	0.19 (0.05-0.70)[a]
Hauth 1983[25]	16 to 20	80	5 (6)	88	5 (5.7)	ND[b]
Controlled Studies Outside US						
Papiernik-Berkhauer 1970[21]	28 to 32	50	2 (4)	49	9 (18)	0.24 (0.07-0.82)[a]
Yemini 1985[23]	mean 12.2	39	5 (13)	40	14 (35)	0.30 (0.11-0.84)[a]
Suvonnakote 1986[24]	16 to 20	35	5 (14)	39[c]	19 (49)	-- (P=0.0036)

Abbreviations: not determined (ND)

[a] Odds ratios reported in Keirse 1989.

[b] Odds ratio was not determined, but differences in rates of preterm birth were not significant.

[c] Placebo group was not used in this study; the control group received no specific study treatment.

The first study indicating a benefit of 17-HPC to reduce prevent birth was published by LeVine in 1964. This single-center, double-blind study evaluated the use of 17-HPC for prevention of habitual abortion.[20] The primary outcome of interest was spontaneous abortion, but preterm delivery was also reported. To be enrolled in the study, patients were required to have had 3 consecutive spontaneous abortions prior to their present pregnancy. Patients were to have a current pregnancy <16 weeks gestation and have no symptoms of threatened abortion. Patients were alternately assigned to receive weekly injections of either 500 mg 17-HPC or placebo. Fifty-six patients started the study, but the outcomes were reported for only the 30 patients (15 per treatment group) who continued the injections until delivery or 36 weeks gestation. Of the 15 patients treated with 17-HPC, 4 aborted spontaneously and 3 delivered preterm. By comparison, patients treated with placebo had 7 spontaneous abortions and 3 preterm deliveries. Therefore, the rate of delivery at $>37^0$ weeks gestation of a live infant was 53% (8/15) in the 17-HPC group versus 33% (5/15) in the placebo group. The odds ratio for preterm birth determined for this study suggested a benefit of 17-HPC use (0.63 [95% CI: 0.10-4.15]), but the sample size was too small to achieve statistical significance.

Six years later, Papiernik-Berkhauer published the results of a randomized, placebo-controlled trial of 17-HPC for the prevention of preterm labor.[21] A total of 50 pregnant women with a high risk for preterm birth received 250 mg 17-HPC intramuscularly every 3 days starting at 28 to 32 weeks gestation and stopping after 8 doses. Forty-nine women received the placebo on the same schedule. Preterm delivery occurred in 4.1% of the pregnancies in the 17P group and 18.8% of the pregnancies in the placebo group. The odds ratio for preterm birth determined for this study was 0.24 (95% CI: 0.07-0.82), signifying a significant reduction in the incidence of preterm birth with 17-HPC treatment.

Johnson and colleagues published the results of a randomized, double-blind study to evaluate 17-HPC for the prevention of preterm birth in 1975.[22] Qualifying patients had a history of 2 spontaneous abortions, 1 preterm birth, and 1 spontaneous abortion immediately preceding the index pregnancy, or at least 2 preterm births at any previous time. The women received weekly injections of 250 mg 17-HPC or placebo beginning prior to 24 weeks of gestation until 37 weeks of gestation or delivery, whichever occurred first. The primary outcome was delivery <36 weeks gestation. None of the eighteen 17-HPC patients delivered before 36 weeks, whereas 9 (41%) of the 22 placebo patients delivered prematurely ($P<0.01$). The odds ratio for preterm birth determined for this study was 0.19 (95% CI: 0.05-0.70). The mean duration of pregnancy and the mean birthweight were significantly greater in the 17-HPC group (38.6 weeks and 2836 g) compared with the placebo group (35.2 weeks and 2361 g; $P<0.025$), while perinatal mortality rate was significantly lower following 17-HPC treatment (0% compared with 27% in the placebo group; $P<0.05$).

Yemini and colleagues published the results of a randomized, double-blind, placebo-controlled study to evaluate 17-HPC for prevention of preterm birth in 1985.[23] Eighty pregnant women who had a history of at least 2 spontaneous abortions, 2 preterm births, or a combination of these were randomized to receive weekly intramuscular injections of either 250 mg 17-HPC or placebo from study entry (mean gestational age at study

enrollment was 12.2 weeks) until 37 weeks gestation or delivery. Baseline characteristics and obstetric histories were similar between the treatment groups, with the exception of a higher number of induced abortions in the 17P group (1.8 compared with 1.4 in the placebo group; $P<0.01$). This trial differs from others in that all patients received a cervical cerclage, but the results still support the use of 17-HPC to reduce the risk of preterm delivery. The rate of preterm births was significantly lower in the17-HPC group (16.1%) than in the Placebo group (37.8%; $P<0.05$), as was the rate of threatened preterm labor (29.0% vs 59.4%; $P<0.025$). The odds ratio for preterm birth determined for this study was 0.30 (95% CI: 0.11-0.84). Mean birth weights were significantly higher in the 17-HPC group (3112 g) compared with the placebo group (2680 g, $P<0.05$), and infants born in the 17-HPC had fewer neonatal morbidities. There were no reported cases of perinatal death or fetal malformations in either group, though the rate of miscarriages was higher in the 17-HPC group (20.4%) than in the placebo group (7.5%).

Suvonnakote and colleagues published the results of a nonrandomized study that evaluated the use of 17-HPC to prevent preterm labor in high-risk patients in 1986.[24] Seventy-five pregnant women with a past history of unsuccessful pregnancies (1 preceding preterm birth, at least 2 previous mid-trimester abortions, or a mixture of term, preterm births, and mid-trimester abortions) were either administered 250 mg 17-HPC (n=36) or placed in the control group and given no study drug (n=39). 17-HPC was administered weekly beginning at 16 to 20 weeks gestation until 37 weeks gestation or until symptoms of labor were established. The percentage of women with preterm births was significantly lower in the 17-HPC group (14% [5/35]) compared with the untreated group (49% [19/39]; $P=0.0036$). The 17-HPC group also had a higher percentage of infants (68.6%) with birth weight >2500 g compared with the untreated group (51.3%), but the difference was not statistically significant ($P=0.2022$). The lack of randomization and of a placebo control diminishes the value of this study, but the results support the benefit of using 17-HPC to reduce the risk of preterm birth.

Among the published studies in singleton pregnancies, only 1 failed to show a benefit of 17-HPC in reducing preterm birth. Hauth and colleagues performed a double-blind trial designed to prospectively evaluate pregnant women in a US active-duty military population and to collect data both on the risks of pregnancy complications and the efficacy of 17-HPC for prevention of preterm labor.[25] Active-duty women from 16 to 20 weeks gestation were analyzed in 1 of 3 groups: 80 who received 1000 mg 17-HPC weekly until 36 weeks gestation; 88 who received placebo consisting of castor oil, 46% benzyl benzoate, and 2% benzyl alcohol; and 78 who declined to participate in the protocol. The 3 groups were similar for parity, history of previous abortion, race, cigarette smoking, and marital status. There were no significant differences in the 3 groups when comparisons were made for low-birth weight infants, perinatal mortality, and the incidence of preterm delivery. The incidence of preterm delivery in the 17-HPC group, placebo group, and declined-to-participate group were 6.3%, 5.7%, and 10.2%, respectively. The lack of effectiveness demonstrated in this study may have been the result of evaluating a relatively low risk population of women who did not all have a history of spontaneous preterm delivery.

In conclusion, despite small sample sizes and differences in study methodologies and treatment regimens, the historical clinical trials provide supportive evidence of the effectiveness of 17-HPC in preventing preterm birth.

4.2.2 Meta-Analyses of Progesterones for Prevention of Preterm Birth

Meta-analyses of the published data also support the use of 17-HPC for prevention of preterm birth.[1,16,64,65,66] Keirse performed a meta-analysis published in 1990 that focused only on trials that employed 17-HPC.[16] The odds ratio for 17-HPC to reduce preterm birth was 0.5 (95% confidence interval [CI] 0.30–0.85), indicating a significant reduction in the risk of preterm birth following 17-HPC treatment. Likewise, significant reductions in the odds of preterm labor (0.43 [95% CI 0.20-0.89]) and birth weight <2500 g (0.46 [95% CI 0.27-0.80]) were also observed following 17-HPC use.

Three subsequent meta-analyses that included the NICHD data published by Meis and colleagues also support the conclusion that 17-HPC is effective in preventing preterm birth.[64,65,66] As shown in Table 4-12, the relative risk of experiencing preterm birth $<37^0$ weeks gestation or an infant weighing <2500 g when treated with 17-HPC versus placebo was very similar whether the meta-analysis included only the earlier 17-HPC studies or if the meta-analysis included Study 17P-CT-002 data. This consistency is striking considering that the earlier studies were all small (sample sizes between 30 and 168 patients) compared with Study 17P-CT-002 (463 patients). These data strongly support the efficacy of 17P in reducing preterm birth and the incidence of low weight (<2500 g) infants. The data also suggest a reduction in perinatal mortality following maternal treatment with 17P, but too few data were available to achieve statistically significance.

Table 4-12. Results of Meta-Analyses of the Effects of 17-HPC

Outcome	Meta-Analysis	Relative Risk 17-HPC vs Placebo	95% Confidence Interval
Preterm birth <37^0 wks gestation	Keirse 1990	0.5	0.30 - 0.85
	Dodd 2005[a]	0.59	0.48 – 0.70
	Sanchez-Ramos 2005[a]	0.48	0.35 – 0.66
	Mackenzie 2006[a]	0.57	0.36 – 0.90
Infant birth weight <2500 g	Keirse 1990	0.46	0.27 - 0.80
	Dodd 2005[a]	0.62	0.49 – 0.78
	Sanchez-Ramos 2005[a]	0.50	0.36 – 0.71
	Mackenzie 2006[a]	0.66	0.51 – 0.87
Perinatal mortality	Keirse 1990	NR	NR
	Dodd 2005[a]	0.60	0.32 – 1.12
	Sanchez-Ramos 2005[a]	0.69	0.38 – 1.26
	Mackenzie 2006[a,b]	0.55	0.14 – 2.15

Abbreviations: not reported (NR)

[a] Included data for Study 17P-CT-002 as published in Meis 2003.[1]

[b] Includes only data from Study 17P-CT-002.

In summary, meta-analyses of earlier studies produced similar relative risk reductions before and after Study 17P-CT-002 data were included, further supporting the consistency of the observation that 17-HPC can prevent recurrent preterm births.[16,64,65,66]

5. SAFETY EVALUATION

5.1 SAFETY OF 17P IN NICHD CLINICAL STUDIES

As previously described, safety data from both Study 17P-IF-001 and Study 17P-CT-002 were integrated into one database for a comprehensive assessment of the safety of 17P.

5.1.1 Extent of Exposure

A total of 613 pregnant women were randomized and received at least 1 injection of study drug in Studies 17P-IF-001 and 17P-CT-002: 404 received 17P and 209 received placebo. Across the 2 studies, 336 women completed the full course of therapy with 17P (ie, weekly injections from study entry until 36^6 weeks of gestation or birth, whichever occurred first). Table 5-1 presents dosing information for Studies 17P-IF-001 and 17P-CT-002, including numbers of injections and patient compliance.

Table 5-1. Dosing Information

	17P	Placebo	*P* value
Study 17P-IF-001	N=65[a]	N=39[a]	
Number of injections			
Mean (SD)	13.3 (5.9)	11.3 (6.2)	0.1497[b]
Min, Max	1, 21	1, 20	
Greater than 90% compliance			
n (%)	54 (83.1)	26 (66.7)	0.0545[c]
Study 17P-CT-002	N=310	N=153	
Number of injections			
Mean (SD)	14.1 (5.6)	13.7 (5.0)	0.1781[b]
Min, Max	1, 21	2, 21	
Greater than 90% compliance			
n (%)	271 (87.4)	134 (87.6)	0.9604[c]

Note: Compliance was defined as the number of injections received divided by the number of expected injections multiplied by 100.

[a] Only includes patients who were not withdrawn from the study due to study termination.

[b] *P* value is from the Wilcoxon rank sum test.

[c] *P* value is from the chi-square test.

5.1.2 Pregnancy Complications

The occurrence of pregnancy-related procedures and pregnancy-related complications was similar for patients treated with 17P and patients treated with placebo (Table 5-2). Among the pregnancy-related procedures, admission to the hospital or labor and delivery unit for preterm labor prior to hospitalization for the actual delivery was experienced by 14.8% of the 17P patients and 15.6% of the placebo patients. The most common

pregnancy complications (those reported by >5% of patients) were preeclampsia or gestational hypertension and gestational diabetes. No significant differences between groups were observed.

Table 5-2. Pregnancy Complications and Maternal Outcomes

Complication or Outcome	17P N=399[a] n (%)	Placebo N=205[a] n (%)	*P* value
Hospital or labor/delivery admission for preterm labor	59 (14.8)	32 (15.6)	0.7834[c]
Gestational diabetes	25 (6.3)	7 (3.4)	0.1792[d]
Oligohydramnios	13 (3.3)	3 (1.5)	0.2851[d]
Significant antepartum bleeding	10 (2.5)	7 (3.4)	0.5654[c]
Preeclampsia or gestational hypertension	33 (8.3)	9 (4.4)	0.0795[c]
Abruption	7 (1.8)	6 (2.9)	0.3565[c]
Confirmed clinical chorioamnionitis	13 (3.3)	5 (2.4)	0.8011[d]
Cerclage placement	5 (1.3)	3 (1.5)	1.0000[d]
Other complication	10 (2.6)[b]	6 (3.0)[b]	0.7928[d]

[a] Of the 404 patients randomized to 17P and the 209 patients randomized to placebo, data on pregnancy complications and maternal outcomes were available for 399 and 205 patients, respectively.

[b] N=389 for 17P group and N=202 for placebo group.

[c] *P* value is from the Cochran-Mantel-Haenszel statistic.

[d] *P* value is from the Fisher exact test.

5.1.3 Adverse Events

5.1.3.1 Incidence of Adverse Events

Adverse events were reported by a comparable percentage of patients following treatment with 17P and treatment with placebo (Table 5-3). The most common AEs in each of the treatment groups, based on system organ class, were general disorders and administration site conditions, which included injection site reactions. The percentages of patients reporting AEs coded to each system organ class were comparable between the 2 treatment groups.

Table 5-3. Incidence of Adverse Events by System Organ Class

MedDRA System Organ Class	17P N=404 n (%)	Placebo N=209 n (%)
Any Adverse Event [a]	239 (59.2)	118 (56.5)
General Disorders and Administration Site Conditions	195 (48.3)	94 (45.0)
Skin and Subcutaneous Tissue Disorders	75 (18.6)	34 (16.3)
Gastrointestinal Disorders	35 (8.7)	17 (8.1)
Injury, Poisoning and Procedural Complications	26 (6.4)	20 (9.6)
Nervous System Disorders	19 (4.7)	5 (2.4)
Pregnancy, Puerperium and Perinatal Conditions	16 (4.0)	6 (2.9)
Musculoskeletal and Connective Tissue Disorders	9 (2.2)	6 (2.9)
Congenital, Familial and Genetic Disorders	9 (2.2)	4 (1.9)
Metabolism and Nutrition Disorders	6 (1.5)	8 (3.8)

Note: Table presents system organ classes in which at least 2% of patients experienced an adverse event.

[a] Patients reporting a particular AE more than once were counted only once for that AE. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 8.0.

Injection site reactions were the most commonly reported adverse events in both treatment groups (Table 5-4). Individual injection site reactions reported by ≥2% of patients in at least 1 treatment group included: pain; swelling; pruritus; nodule; and irritation. Swelling was the only injection site reaction that was reported by significantly (P=0.0055) more patients in the 17P group than in the placebo group.

Table 5-4. Most Frequently Reported Adverse Events

Preferred Term	17P N=404 n (%)	Placebo N=209 n (%)
Any adverse event[a]	239 (59.2)	118 (56.5)
Injection site reactions:	180 (44.6)	85 (40.7)
Injection site pain	149 (36.9)	74 (35.4)
Injection site swelling	68 (16.8)	18 (8.6)
Injection site pruritus	25 (6.2)	10 (4.8)
Injection site nodule	17 (4.2)	7 (3.3)
Injection site irritation	5 (1.2)	5 (2.4)
Urticaria	51 (12.6)	24 (11.5)
Pruritus	28 (6.9)	11 (5.3)
Contusion	26 (6.4)	20 (9.6)
Nausea	20 (5.0)	8 (3.8)
Vomiting	11 (2.7)	6 (2.9)
Death[b]	10 (2.5)	9 (4.3)
Diarrhea	9 (2.2)	1 (0.5)
Edema	8 (2.0)	2 (1.0)
Abdominal pain	6 (1.5)	6 (2.9)
Anorexia	5 (1.2)	7 (3.3)

Note: Table presents adverse events experienced by at least 2% of patients in either treatment group.

[a] Patients reporting a particular AE more than once were counted only once for that AE. AEs were coded using MedDRA Version 8.0.

[b] The MedDRA coding included only the neonatal deaths under this preferred term. Miscarriages and stillbirths were coded to other preferred terms and were experienced by less than 2% of patients in each treatment group.

5.1.3.2 Adverse Events Leading to Discontinuation

The rate of early discontinuations of study drug due to AEs was comparable in the 17P (2.2%) and placebo groups (3.3%) (Table 5-5). Injection site reactions were the adverse events most commonly leading to discontinuation in both groups.

Table 5-5. Adverse Events Leading to Discontinuation

Preferred Term	17P N=404 n (%)	Placebo N=209 n (%)
Discontinued due to any AE	9 (2.2)	7 (3.3)
Injection site reactions	4 (1.0)	3 (1.4)
Allergic reaction	1 (0.2)	1 (0.5)
Urticaria	2 (0.5)	1 (0.5)
Pruritus	0	2 (1.0)
Weight gain	1 (0.2)	0
Arthralgia	1 (0.2)	0

5.1.3.3 Serious Adverse Events

Serious adverse events in the 17P-IF-001 and 17P-CT-002 studies were collected in accordance with NICHD MFMU practices. Specifically, all deaths (maternal, fetal, or neonatal) and life-threatening events required completion of a written safety report using the MFMU Network AE Form. In addition, adverse events that were serious and unexpected in nature, severity, or frequency also required completion of the MFMU Network AE Form.

Serious adverse events were reported by a comparable percentage of patients in the 2 treatment groups (Table 5-6). The most common SAEs were neonatal deaths, stillbirths, and miscarriages (discussed in Section 5.1.3.3.1) and congenital anomalies (discussed in Section 5.1.3.3.2).

Table 5-6. Serious Adverse Events by Preferred Term – Maternal, Fetal, and Neonatal Events

Preferred Term[a]	17P N=404 n (%)	Placebo N=209 n (%)
Any SAE and unexpected AE	38 (9.4)	22 (10.5)
Maternal		
Injection site reactions[b]	4 (1.0)	2 (1.0)
Respiratory distress	1 (0.2)	0
Choking	1 (0.2)	0
Hypersensitivity	1 (0.2)	0
Cellulitis	1 (0.2)	0
Endometritis	1 (0.2)	0
Arthralgia	1 (0.2)	0
Uterine rupture	1 (0.2)	0
Pulmonary embolism	1 (0.2)	0
Adverse drug reaction	0	1 (0.5)
Pruritus	0	1 (0.5)
Neonatal/Fetal		
Death[c]	10 (2.5)	9 (4.3)
Stillbirth	7 (1.7)	4 (1.9)
Miscarriage	6 (1.5)	1 (0.5)
Congenital anomalies	9 (2.2)	4 (1.9)
Testicular infarction	1 (0.2)	0

[a] SAEs and unexpected AEs reported on the MFMU Network AE Form were coded using MedDRA Version 8.0.

[b] Injection site reaction is the higher level term; the incidences by preferred terms of injection site reactions reported on the MFMU Network AE Form were also not different between treatment groups.

[c] The MedDRA coding included only the neonatal deaths under this preferred term. Miscarriages and stillbirths were coded separately.

5.1.3.3.1 Deaths

The overall rate of combined fetal and neonatal deaths was comparable between the 2 treatment groups (Table 5-7). None of the fetal or neonatal deaths were considered by the investigator to be related to study drug. While the overall incidence of miscarriage was comparable based on the integrated data, there was a higher rate of miscarriage in the 17P group in Study 17P-CT-002. In that study, 5 of the 310 patients (1.6%) in the 17P group had miscarriages compared with none of the 153 patients in the placebo group ($P>0.05$). None of the individual miscarriages were considered by the investigator to be related to the use of 17P and appeared more related to prior pregnancy history, pregnancy

complications, and social factors than study drug. Specifically, 2 of the women who miscarried had threatened abortions prior to being randomized at 17^3 or 17^5 weeks of gestation and received only 1 injection of 17P before the event. One of these women was a cocaine user who had gone through rehabilitation during the study pregnancy (1 month before being randomized). A third woman developed bacterial vaginosis, experienced preterm premature rupture of membranes at 18^6 weeks after 3 injections of 17P, and chose to terminate the pregnancy.

In summary, while the incidence of miscarriage was higher following 17P treatment, none were considered related to administration of 17P. The overall rate of miscarriages across the 2 studies was low considering that approximately one-third of the women reported having at least 1 previous miscarriage. Additionally, the overall rate of miscarriage reported in this study was lower than that previously reported by Mercer et al, who noted a 3.9% second-trimester miscarriage rate was among 1711 multiparous women with a history of least 1 prior preterm birth.[6]

Table 5-7. Fetal and Neonatal Deaths

Fetal/Neonatal Deaths	17P N=404	Placebo N=209	*P* value[a]
Miscarriages, n (%)	6 (1.5)	1 (0.5)	0.2629
Stillbirths, n (%)	7 (1.7)	4 (1.9)	0.8769
Neonatal deaths, n (%)	10 (2.5)[b]	9 (4.3)[c]	0.1928
TOTAL	23 (5.7)	14 (6.7)	0.5977

[a] *P* value is from the Cochran-Mantel-Haenszel statistic.

[b] Percentage based on all randomized 17P patients; the rate for liveborn infants was 2.6% (10/386).

[c] Percentage based on all randomized placebo patients; the rate for liveborn infants was 4.5% (9/202).

5.1.3.3.2 Congenital Anomalies

The percentage of infants with congenital abnormalities identified at birth across the 2 studies was comparable between the 2 treatment groups. The types of congenital anomalies were not different between treatment groups and the majority were congenital anomalies that are known to occur during embryogenesis in the first trimester, ie, before women qualified to receive the first injection of study drug (at least 16 weeks of gestation). Specific details of the congenital anomalies identified at birth are provided in Table 5-8.

Table 5-8. Congenital Anomalies Identified at Birth

Patient ID	Treat-ment	GA at first injection	Number of injections	GA at birth	Sex	Event(s) of Interest
Study 17P-IF-001						
002-005	17P	17^{0}	3	40^{6}	male	Breast malformation
014-001	17P	19^{2}	15	34^{2}	male	Limb reduction defect (transverse deficiency of upper limb)
015-001	17P	19^{3}	16	39^{1}	male	Hydrocele of tunica vaginalis
015-004	Placebo	20^{5}	12	35^{3}	male	Hydrocele of tunica vaginalis
Study 17P-CT-002						
002-024	17P	19^{2}	3	38^{4}	female	Cardiovascular anomaly (cardiomegaly; diverticulum [left ventricle]; pericardial effect)
014-016	17P	20^{6}	8	38^{1}	male	Genitourinary abnormality (renal pelvis; ureter)
015-015	17P	17^{1}	14	37^{0}	male	Hydrocele of tunica vaginalis
015-025	17P	18^{1}	10	35^{6}	female	Polydactyly (accessory fingers; other talipes calcaneovarus)
015-028	17P	19^{1}	11	30^{4}	male	Cardiovascular anomaly (other circulatory system anomalies)
021-022	17P	18^{1}	18	35^{3}	male	Pes planus, rocker bottom flat foot
002-047	Placebo	20^{6}	7	28^{3}	male	Cardiovascular anomaly (stenosis and other circulatory anomalies); polydactyly (accessory fingers)
004-046	Placebo	20^{2}	16	39^{0}	male	Genitourinary abnormality (bladder; urethra)
021-011	Placebo	17^{3}	19	39^{4}	male	Talipes equinovarus

5.1.4 Safety Conclusions from NICHD Studies

The safety results from Studies 17P-IF-001 and 17P-CT-002 demonstrate that administration of 17P was:

- safe and well tolerated by pregnant women. Adverse events were reported by a comparable percentage of patients in each group and the rate of discontinuation due to adverse events was low.
- safe for the developing fetus and neonate. The percentage of combined stillbirths, miscarriages, and neonatal deaths was comparable between the 2 treatment groups and the rates of congenital anomalies reported at birth were comparable to those reported in population surveys.

Taken together, the safety results of the 17P-IF-001 and 17P-CT-002 studies indicate that weekly injections of 17P do not pose a significant risk to pregnant women or their developing offspring.

5.2 LONG-TERM INFANT FOLLOW-UP

Long-term follow-up data on the health and development of infants born during the 17P-CT-002 study were collected in the noninterventional Study 17P-FU.

5.2.1 Infant Disposition and Demographics

Only patients enrolled in Study 17P-CT-002 at study sites that were active members of the MFMU Network in 2005 were considered eligible for Study 17P-FU. Based on these criteria, 348 (78%) of the 446 infants born to women enrolled in Study 17P-CT-002 and who survived to be discharged from birth hospitalization were eligible to participate in Study 17P-FU. Among the 234 children exposed to 17P who were eligible for enrollment, 82.9% were enrolled in Study 17P-FU. Likewise, 73.7% of the 114 eligible children exposed to placebo were enrolled. The disposition of children enrolled in the follow-up study is presented in Figure 5-1.

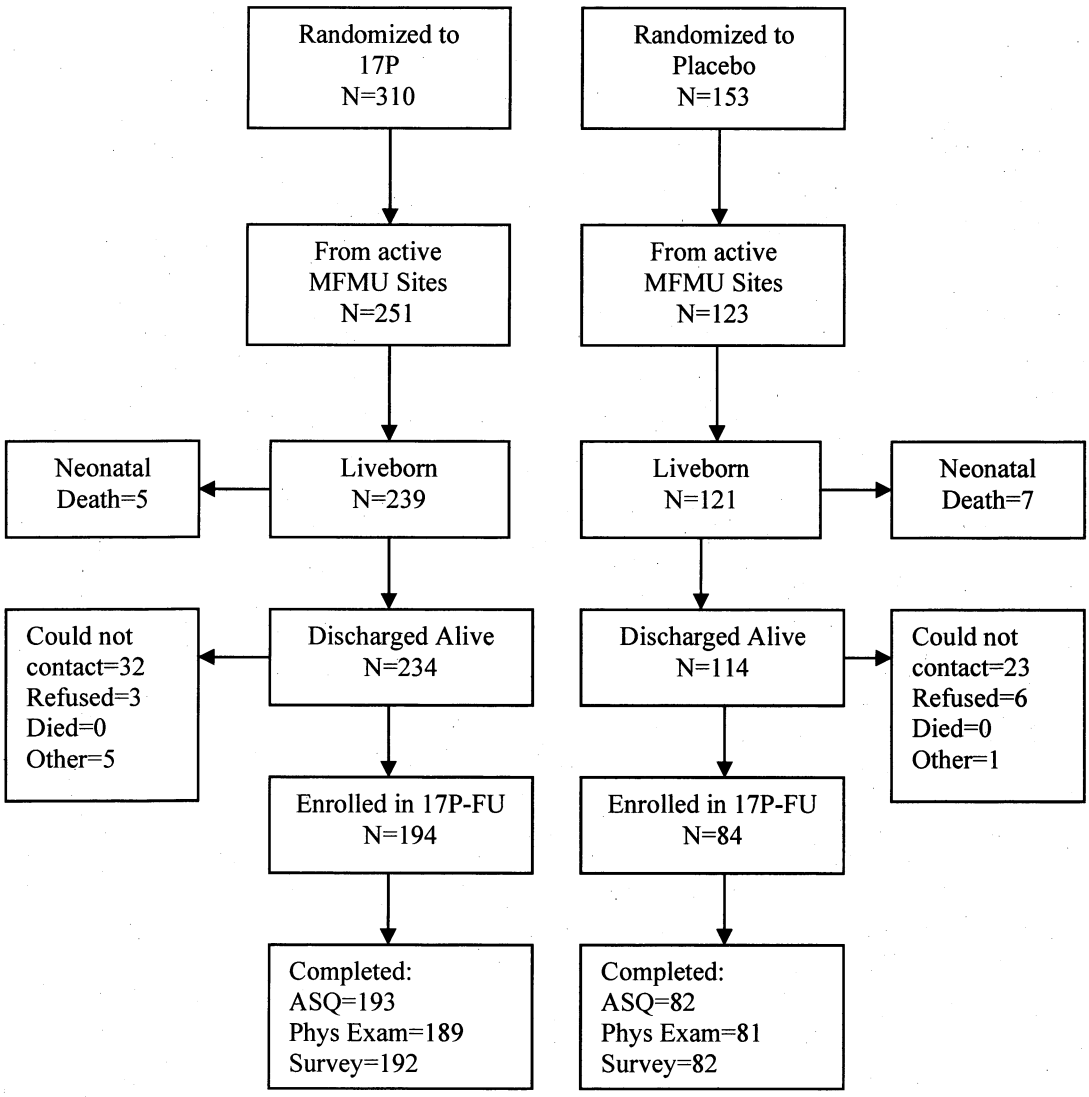


Figure 5-1. Disposition of Children Enrolled in Follow-Up Study

At the time of enrollment in the follow-up study, the demographics of the children enrolled were comparable between the 2 groups (Table 5-9). Children in the 17P group were born at later gestational ages and had a higher mean birth weight than children in the placebo group, which reflects the lower incidence of preterm births in Study 17P-CT-002.

Table 5-9. Demographics of Children Enrolled in Follow-Up Study

Characteristic	17P N=194	Placebo N=84
Age at enrollment (months)		
Mean (SD)	47.2 (8.6)	48.0 (8.3)
Min, Max	30.2, 63.9	33.5, 64.3
Race/Ethnicity, n (%)		
African American	105 (54.1)	47 (56.0)
Caucasian	55 (28.4)	20 (23.8)
Hispanic	29 (14.9)	15 (17.9)
Asian	2 (1.0)	1 (1.2)
Other	3 (1.5)	1 (1.2)
Sex, n (%)		
Male	113 (58.2)	40 (47.6)
Female	81 (41.8)	44 (52.4)
Treatment assignment disclosed, n (%)		
Yes	16 (8.3)	6 (7.1)
Gestational age at birth (wks)		
Mean (SD)	37.3 (3.2)	36.2 (3.7)
Min, Max	25.0, 41.7	25.1, 41.9
Birth weight (g)		
Mean (SD)	2914 (707.8)	2756.7 (813.7)
Min, Max	714, 4900	615, 4855

Among the 278 children enrolled in the follow-up study, the treatment assignment from Study 17P-CT-002 was known by the parent/guardian of 22 children (16 who were exposed to 17P *in utero* and 6 who were exposed to placebo). In these cases, the parent/guardian had knowledge of treatment prior to completing the questionnaires in the follow-up study.

5.2.2 Ages and Stages Questionnaire Results

The primary safety measure in Study 17P-FU used the Ages and Stages Questionnaire (ASQ), a commonly used screening tool to be completed with the parent/guardian that allows identification of children considered to be at medical risk that may require further evaluation and early intervention. The ASQ is composed of questionnaires containing 30 items addressing 5 developmental areas: communication, gross motor, fine motor, problem solving, and personal-social. The ASQ was scored based upon the sum of scores for each question in a category (Yes=10, Sometimes=5, and Not Yet=0). The ASQ uses predefined cut-off points designed to identify children considered to be at medical risk who may require further evaluation and early intervention.

In utero exposure to 17P was not associated with a delay in development based upon ASQ findings. As presented in Table 5-10, the percentage of children who scored below a

specified cutoff for at least 1 developmental area on the ASQ was not significantly different (P=0.9206) between the 17P and placebo groups. The percentages of children who scored below the ASQ cutoff in each of the 5 developmental areas were also comparable between the 17P and placebo groups.

Table 5-10. Ages and Stages Questionnaire

Area of Development	17P N=193 n (%)	Placebo N=82 n (%)	*P* value
Occurrence of score below cutoff on at least 1 area of development	53 (27.5)	23 (28.0)	0.9206[a]
Communication	22 (11.4)	9 (11.0)	0.9191[a]
Gross Motor	5 (2.6)	3 (3.7)	0.6989[b]
Fine Motor	40 (20.7)	15 (18.3)	0.6445[a]
Problem Solving	20 (10.4)	9 (11.0)	0.8797[a]
Personal-Social	7 (3.6)	1 (1.2)	0.4427[b]

[a] *P* value is from the chi-square test.

[b] *P* value is from the Fisher exact test.

5.2.3 Survey Questionnaire Results

In addition to the ASQ, the 17P-FU study utilized a Survey Questionnaire tailored specifically for this study that was comprised of questions that were derived from the following validated instruments: the 2001 Child Health Supplement of the National Health Interview Survey, the 1991 National Maternal and Infant Health Survey, Early Childhood Longitudinal Survey (Department of Education), and the Avon Longitudinal Study of Parents and Children.

The Survey Questionnaire asked the parent/guardian to provide information on the child's gender-specific play (based on the preschool activities inventory [PSAI]), physical growth, activity levels, motor control, vision or hearing difficulties, and any diagnoses since discharge from birth hospitalization that were made by a health professional, such as asthma, allergic disorders, sensory disorders, and neurodevelopmental disorders (attention deficit hyperactivity disorder [ADHD] or attention deficit disorder [ADD]).

Based on the information provided by the parent/guardian on the Survey Questionnaire, no safety concerns related to the use of 17P during pregnancy were identified.

5.2.3.1 Gender Specific Play

There were no differences in gender-specific roles between the 17P and placebo groups (Table 5-11).

Table 5-11. Gender Specific Roles

PSAI	17P	Placebo	*P* value[a]
Number of enrolled children with completed questionnaire	192	82	
PSAI in males, n (%)	112 (58)	39 (48)	
Mean (SD)	66.48 (8.32)	67.28 (10.59)	0.3437
Min, Max	51.55, 90.05	44.74, 90.05	
PSAI in females, n (%)	80 (42)	43 (52)	
Mean (SD)	31.78 (8.45)	33.11 (8.83)	0.5432
Min, Max	10.85, 55.95	14.97, 55.95	

Abbreviations: preschool activities inventory (PSAI)

[a] *P* value is from the Wilcoxon rank sum test.

5.2.3.2 Physical Growth, Motor Skills, and Activity Levels

No significant differences in physical growth, motor skills, or activity levels were observed between the 2 treatment groups (Table 5-12).

Table 5-12. Physical Growth, Motor Skills, and Activity Levels

	17P	Placebo	*P* value[a]
Percentile of normal height (cm)	N=182	N=77	
Mean (SD)	54.4 (29.5)	57.0 (28.9)	--
Min, Max	1.2, 99.7	0.5, 98.5	--
Below normal height, n (%)	7 (3.8)	4 (5.2)	0.7371
Percentile of normal weight (kg)	N=189	N=80	
Mean (SD)	55.2 (29.7)	57.0 (29.6)	--
Min, Max	0.1, 100.0	0.0, 100.0	--
Below normal weight, n (%)	11 (5.8)	6 (7.5)	0.5921
	N=192	N=82	
Diagnosis of problem in overall activity, n (%)	2 (1.0)	1 (1.2)	1.0000
Diagnosis of problem in coordination or use of limbs, n (%)	1 (0.5)	1 (1.2)	0.5097

Note: Ns represent numbers of children included in the assessment based on available data.

[a] *P* value is from the Fisher exact test.

5.2.3.3 Hearing, Vision, and Use of Special Equipment

Results from the Survey Questionnaire on hearing, vision, and the use of special equipment were comparable between the 2 treatment groups (Table 5-13). No significant differences in any finding were noted.

Table 5-13. Hearing, Vision, and Use of Special Equipment

Categories	17P N=192[a] n (%)	Placebo N=82[a] n (%)	*P* value[b]
Hearing			
Good	188 (97.9)	77 (93.0)	0.1327
Little trouble	4 (2.1)	5 (6.1)	0.1327
Lot of trouble	0	0	--
Wears hearing aid	0	0	--
Deaf	0	0	--
Vision			
No trouble seeing	188 (97.9)	80 (97.6)	0.7972
Trouble seeing and wears glasses	3 (1.6)	1 (1.2)	--
Trouble seeing and does not wear glasses	1 (0.5)	1 (1.2)	--
Use of special equipment			
Wheelchair	0	1 (1.2)	0.5097
Brace	1 (0.5)	0	--
Impairment or health problem that limits ability to walk, run, or play	5 (2.6)	5 (6.1)	0.1714

[a] The number of children for whom the Survey Questionnaire was completed; 2 children in each treatment group did not have a completed Survey Questionnaire.

[b] *P* value is from the Fisher exact test.

5.2.3.4 Communication and Problem Solving

No significant differences in results from the Survey Questionnaire on communication and problem solving were reported between the 2 treatment groups (Table 5-14). Mental retardation was reported for 1 child in the 17P group who had Down syndrome and autism.

Table 5-14. Communication and Problem Solving

	17P N=192[a]	Placebo N=82[a]	*P* value[b]
Diagnosis of problem in ability to communicate, n (%)	9 (4.7)	7 (8.5)	0.2605
Age at first diagnosis (months)			
Mean (SD)	17.6 (14.55)	16.7 (11.87)	--
Median	12	12	
Min, Max	0.0, 48.0	1.0, 36.0	--
Diagnosis of problem in ability to pay attention/learn, n (%)	8 (4.2)	5 (6.1)	0.5387
Learning disability	1 (0.5)	0	--
ADHD or ADD	1 (0.5)	2 (2.4)	--
Developmental delay[c]	5 (2.6)	3 (3.7)	--
Autism or pervasive developmental disorder	1 (0.5)	0	--
Mental retardation	1 (0.5)	0	--
Other	2 (1.0)	1 (1.2)	--
Age at first diagnosis (months)	N=8	N=4	
Mean (SD)	22.4 (20.80)	18.3 (15.11)	--
Median	12	18	
Min, Max	0.0, 60.0	1.0, 36.0	--

Abbreviations: attention deficit hyperactivity disorder (ADHD); attention deficit disorder (ADD)

[a] The number of children for whom the Survey Questionnaire was completed; 2 children in each treatment group did not have a completed Survey Questionnaire.

[b] *P* value is from the chi-square or Fisher exact test.

[c] Parent/guardian reported a diagnosis of developmental delay specific to the child's ability to pay attention, learn, think, and problem solve.

5.2.3.5 Overall Health

The overall health was comparable between the 17P and placebo groups (Table 5-15). There were lower rates of chronic (>3 months) medication use and lower surgical interventions in the 17P group, but the differences were not statistically significant.

Table 5-15. Overall Health

	17P N=192[a] n (%)	Placebo N=82[a] n (%)	*P* value
Overall health			0.4797[b]
Excellent	117 (60.9)	46 (56.1)	--
Very good	43 (22.4)	22 (26.8)	--
Good	28 (14.6)	10 (12.2)	--
Fair	4 (2.1)	4 (4.9)	--
Compared to 12 months ago, health is:			0.6930[c]
Better	64 (33.3)	26 (31.7)	--
Worse	2 (1.0)	2 (2.4)	--
About the same	126 (65.6)	54 (65.9)	--
Health problem requiring medication for ≥3 months	21 (10.9)	16 (19.5)	0.0572[b]
Any operations	23 (12.0)	17 (20.7)	0.0602[b]
Hernia repair	4 (2.1)	2 (2.4)	--
Surgery for undescended testicles	1 (0.5)	0	--
Ear tubes inserted	8 (4.2)	7 (8.5)	--
Tonsils removed	5 (2.6)	1 (1.2)	--
Adenoids removed	5 (2.6)	1 (1.2)	--
Other	7 (3.6)	7 (8.5)	--

[a] The number of children for whom the Survey Questionnaire was completed; 2 children in each treatment group did not have a completed Survey Questionnaire.

[b] *P* value is from the chi-square test.

[c] *P* value is from the Fisher exact test.

5.2.3.6 Reported Diagnoses by Health Professionals

The incidence of reported diagnoses as communicated by the parent/guardian on the Survey Questionnaire was comparable between children exposed to 17P and children exposed to placebo (Table 5-16). Of note, developmental delay, defined as a reported diagnosis by a health professional that the child was falling significantly behind age-mates in physical, mental, social/emotional, or speech development, was reported for a comparable percentage of children in the treatment groups.

Table 5-16. Reported Diagnoses by Health Professionals

Reported Diagnosis	17P N=192[a] n (%)	Placebo N=82[a] n (%)
Asthma	39 (20.3)	20 (24.4)
Asthma attack in past 12 months	20 (10.4)	8 (9.8)
Visit to ER or Urgent Care due to asthma in past 12 months	18 (9.4)	7 (8.5)
Eczema or skin allergy	35 (18.2)	12 (14.6)
Ear infections (3 or more)	20 (10.4)	7 (8.5)
Hay fever	19 (9.9)	5 (6.1)
Respiratory allergy	16 (8.3)	9 (11.0)
Developmental delay	14 (7.3)	7 (8.5)
Stuttering or stammering[b]	11 (6.4)	5 (6.6)
Frequent repeated diarrhea or colitis	5 (2.6)	1 (1.2)
Anemia	5 (2.6)	4 (4.9)
Food or digestive allergy	3 (1.6)	3 (3.7)
Seizures or convulsions with fever	3 (1.6)	1 (1.2)
Frequent or severe headaches or migraines	1 (0.6)	2 (2.6)
Diabetes	1 (0.5)	0
Arthritis	1 (0.5)	0
Seizures or convulsions without fever	0	1 (1.2)
Cerebral palsy	0	1 (1.2)
Sickle cell	0	1 (1.2)

Abbreviations: emergency room (ER)

[a] The number of children for whom the Survey Questionnaire was completed; 2 children in each treatment group did not have a completed Survey Questionnaire.

[b] Question answered only for children 3 years or older. Percentages were based on N=171 in 17P group and N=76 in placebo group.

5.2.4 Physical Examination Findings Including Genital and Reproductive Anomalies

As part of the follow-up study, a general physical examination was conducted by a pediatrician or nurse practitioner at the study center. These examinations included measurements of the child's current weight, height, head circumference, and blood pressure. While women in Study 17P-CT-002 received 17P beginning only in the second trimester, a time after which major congenital abnormalities would be expected to occur[67], the follow-up physical examination still targeted major physical abnormalities. Specific emphasis was placed on genital abnormalities. If the child was unable to attend the study visit, information from a previous physical examination (within 1 year) was abstracted from the child's medical records.

Physical examinations findings were comparable between the 17P infants and the placebo infants (Table 5-17). The most common abnormalities were of the skin and palpable inguinal nodes. Minor heart conditions, such as murmurs and irregular heart rhythm,

were identified in 5% of the 17P group and 0% in the placebo group; the imbalance between groups was considered random chance since the incidence of murmurs in young children has been reported to be as high as 50%.[68]

Table 5-17. Follow-Up Study Physical Examination Results

Abnormality or Location of Abnormality	17P N=194	Placebo N=84
Skin, N	187	80
n (%)	23 (12.3)	6 (7.5)
Inguinal nodes palpable, N	184	80
n (%)	20 (10.9)	7 (8.8)
Mouth, N	187	81
n (%)	17 (9.1)	7 (8.6)
Neck, N	187	81
n (%)	11 (5.9)	4 (4.9)
Heart, N	188	81
n (%)	10 (5.3)	0
Ears,	188	81
n (%)	6 (3.2)	3 (3.7)
Supraclavicular nodes palpable, N	184	80
n (%)	6 (3.3)	2 (2.5)
Kidneys palpable, N	186	79
n (%)	4 (2.2)	0
Rhythm by auscultation, N	188	80
n (%)	3 (1.6)	0
Legs, N	188	80
n (%)	2 (1.1)	1 (1.3)
Epicanthal folds, N	185	77
n (%)	2 (1.1)	1 (1.3)

Medical events of special interest among the infants born during the 17P-CT-002 study included genital or reproductive anomalies identified upon physical examination or upon review of the completed Survey Questionnaire. During the follow-up study, 5 (2.6%) children in the 17P group and 1 (1.2%) child in the placebo group had genital or reproductive anomalies reported. These 6 children with reported anomalies are listed in Table 5-18.

Table 5-18. Genital and Reproductive Anomalies Identified During Follow-up Safety Assessments

Patient ID	Treat-ment Group	GA at first injection	Number of Injections	GA at birth	Sex	Event(s) of Interest	Age at FU Assessment (mo)
018-032	17P	20^{4}	7	38^{1}	female	Clitoral hypertrophy	48.8
020-023	17P	17^{0}	21	38^{1}	female	Labioscrotal fusion	60.3
025-002	17P	20^{0}	17	39^{6}	female	Early puberty at 3.5 yr of age	43.4
008-167	Placebo	18^{0}	7	25^{1}	female	Sparse pubic hair at 3.4 yr of age	41.7
008-076	17P	19^{0}	18	38^{1}	male	Micropenis; small scrotal sac	54.1
008-134	17P	18^{2}	14	33^{5}	male	Micropenis; Down syndrome	42.4

Abbreviations: gestational age (GA); follow-up (FU)

Two females had abnormalities of the genitalia noted, both in the 17P group. One female child was reported to have clitoral hypertrophy and another female child was reported to have labioscrotal fusion. For the child reported to have clitoral hypertrophy, the maternal birth and newborn records indicated that all assessments of genitalia were within normal limits. A repeat physical examination 4 months later by the same physician who performed the follow-up study physical examination found the female genitalia to be normal (clitoris <5 mm in transverse diameter). For the child reported to have labioscrotal fusion, the maternal birth records, newborn records, and ambulatory pediatric records from 1 week to 3 years of age were reviewed. The newborn assessment as well as pediatric records at 1, 4, 6, 9, 12, 15, 18, and 24 months all indicated that genitalia were within normal limits.

Signs of early puberty were reported for 1 female child in the 17P group. At 3.6 years of age, the child had breast buds (4-5 cm) noted during the physical examination and joint pain reported by the mother on the Survey Questionnaire that she considered related to early puberty. Potentially confounding the determination of breast development during the physical examination was the child's weight of 30 kg, which at a height of 107 cm placed her in the 100^{th} percentile for body mass index. Medical records revealed no abnormalities on physical examination at birth.

One female child in the placebo group had sparse pubic hair present at the time of the study physical examination, when she was 3.5 years of age. This child was born preterm at 25 weeks of gestation and had a protracted NICU stay, with no physical abnormalities noted at birth.

Two male infants in the 17P group and none in the placebo group were reported to have a small penis. Based upon review of all data, these events did not appear to be treatment related. The male child with the micropenis also had Down syndrome, a syndrome in which micropenis is not uncommon.[69,70] The second child was reported to have a small penis at 4.5 years of age. In this child's newborn medical records, 2 comments were made under Genitalia: "male – meatus present and testes palpable." No other comments were made regarding abnormalities of size or structure of the penis, testes, or scrotal sac.

Based upon review of all available data for these children, it is concluded that *in utero* exposure to 17P was unlikely to have contributed to any of the genital abnormalities reported.

5.2.5 Safety Conclusions from Follow-Up Study

The safety results from the long-term follow-up Study 17P-FU demonstrate that *in utero* exposure to 17P:

- does not lead to delay in development. The results from the ASQ demonstrated no significant differences between the 2 groups in the percentage of children falling below cutoffs for any developmental area.
- does not pose any safety concerns related to overall health or physical development. The results from the Survey Questionnaire demonstrated no significant differences between the 2 groups in any assessment, including gender-specific roles.
- is not associated with the development of genital or reproductive anomalies. While 2.6% of children in the 17P group were noted to have genital or reproductive anomalies abnormalities upon physical examination compared with 1.2% in the placebo group, none were considered to be associated with *in utero* exposure to 17P based on the nature of the physical finding, the gestational age at first exposure, or the presence of other likely contributing factors.

Taken together, the results of the NICHD 17P-FU study indicate that *in utero* exposure to 17P has no untoward effects on developmental milestones or physical health status of children.

5.3 SAFETY OF 17-HPC USE IN SCIENTIFIC LITERATURE

5.3.1 Clinical Trials and Epidemiological Studies

The safety of 17-HPC use in pregnancy is further supported by multiple scientific publications of controlled studies. As previously discussed, multiple studies have evaluated the effectiveness of 17-HPC for the prevention of preterm birth in singleton pregnancies.[20,21,22,23,24] In these studies, the publications consistently noted that

administration of 17-HPC was not associated with maternal adverse effects other than discomfort or tenderness at the injection site. Overall, the publications did not suggest that 17-HPC exposure was associated with an excess rate of fetal or neonatal death. Rates of perinatal morbidity were not higher following 17-HPC treatment and were noted to be significantly reduced relative to the placebo group in one study.[22] One study noted that the percentage of live births was significantly higher following 17-HPC treatment, while another study noted that the miscarriage rate was significantly higher in the 17-HPC group.[20,23] Only 2 of the studies noted any observed abnormalities among infants at birth, but none of the abnormalities noted (anencephaly, accessory digits of the hand) were considered related to 17-HPC exposure by the authors.[22,24]

A number of published studies have examined the effects of *in utero* exposure of 17-HPC on the developing fetus. These studies include assessments of congenital anomalies and psychological development. The results from these studies support the findings that 17-HPC is not teratogenic and is safe for the developing fetus.[26,27,28,29,71]

Varma and Morsman conducted a retrospective evaluation of the safety of 17-HPC administered for prevention of threatened abortion.[26] Over a period of 7 years, 150 patients received weekly intramuscular injections of 17-HPC (250 to 500 mg) from 6 to 8 weeks up to 16 to 18 weeks of gestation. These patients were matched with control patients who did not receive hormone treatment. No evidence was found that 17-HPC had any adverse effect on the outcome of the pregnancy or the fetus. The rate of fetal anomalies was 0.7% in the 17-HPC group versus 2.0% in the control group. One infant in the 17-HPC group had a proven fetal anomaly (infant stillborn at 33 week gestation with hydrocephalus and other anomalies) compared with 3 infants (anencephaly, spina bifida, and multiple anomalies) in the control group. No incidence of masculinization of female infants was observed.

Resseguie and colleagues examined the medical records of 24,000 women to identify children who were exposed to sex hormones *in utero*.[27] A total of 649 children were identified that been exposed to 17-HPC. The median time of first exposure was 60 days of gestation and the median total exposure was estimated to be 1625 mg. No differences in the frequency or type of congenital anomalies were observed between children exposed to 17-HPC *in utero* and unexposed children. The incidence of any major anomaly was 5.5% among children exposed to 17-HPC *in utero* compared with 4.5% among unexposed children. Children exposed to 17-HPC had comparable rates of genitourinary anomalies, central nervous system anomalies, major cardiovascular anomalies, and hypospadias compared with the control group. A notable feature of this study was the long period of follow-up of the children, with a mean of 11.5 years. The results from this study supported the observation that progestin exposure and the occurrence of anomalies were independent events, even if only first-trimester exposure was considered.

In a cohort study of 13,643 pregnancies in West Germany, Michaelis and colleagues found no increase in malformations in infants exposed *in utero* to 17-HPC during the first trimester.[28] The study evaluated women treated with progesterone and 17-HPC to prevent abortion. Ten major malformations were observed in infants delivered among 462 women

who received 17-HPC (2.2%). Of these 10, there were 6 whose mothers received one or more other sex hormones in addition to 17-HPC and 4 whose mothers received 17-HPC only. No major malformations were observed in infants delivered by 186 women who received progesterone. Women who received only progesterone or 17-HPC during the first 12 weeks (n=320) were combined and compared with selected controls in a matched-pair analysis. The number of major malformations was not increased in the active group (4 infants) compared with the control group (6 infants). The number of miscarriages was increased in the active group; however, this was to be expected since those women receiving progesterone treatment were those at higher risk for abortion.

Katz and colleagues compared 1608 infants who were exposed to progestogens during the first trimester of pregnancy to 1146 control infants delivered at the same hospital to examine the potential teratogenicity of progestogens.[29] The progestogens studied were oral medroxyprogesterone acetate administered at doses of 20 to 30 mg per day, 17-HPC administered as weekly injections of 500 mg, or a combination of the 2 drugs. The overall rate of malformations was not different between the progestogen group (120/1000) and the control group (124/1000). The authors concluded that there was no evidence of teratogenicity due to progestogens administered during the first trimester of pregnancy.

The long-term impact of *in utero* exposure to 17-HPC on psychological development has also been examined. Kester examined adolescent males exposed to 17-HPC to determine whether prenatal exposure impacted recreational interests and psychosexual development in boyhood.[71] Twenty-five males exposed to 17-HPC and closely matched unexposed controls were evaluated based on a number of psychological tests. No significant differences in psychological testing were noted for adolescents exposed to 17-HPC. The total dosage of 17-HPC, duration of exposure, and period of gestation had no significant impact on the findings.

In summary, the published literature provides no evidence that administration of 17-HPC during pregnancy results in significant risk to mother, fetus, or newborn. Importantly, epidemiological studies evaluating first trimester exposure demonstrate a lack of association between the use of 17-HPC and the incidence of congenital anomalies. Major congenital anomalies are unlikely to occur from drug exposure later than the first trimester of pregnancy, the time of organogenesis.[67] The proposed indication for 17P is to initiate treatment no earlier than 16 weeks of gestation, after the period of most vulnerability for the fetus. This timing further reduces any safety concern for the fetus.

5.3.2 FDA Assessment of Congenital Anomalies

The conclusion that exposure to 17P is not teratogenic is supported by the published findings of the FDA. The FDA conducted a thorough scientific review of all available data regarding the association between progesterone use and congenital malformations. The review was conducted to determine whether drugs containing natural progesterone or synthetic progestins should still carry a class warning about their use during the first trimester of pregnancy. At the conclusion of their review, the FDA proposed a rule in the 13 April 1999, *Federal Register*, that there was no need for special labeling.[72]

During their review, the FDA noted that most cases associating progestogen use during pregnancy with virilization of the genitalia in female infants involved high doses of ethisterone and norethindrone, both of which are androgen-derived progestins. They concluded that a warning of an increased risk of birth defects for all progestogens is not warranted and that:

> *"The reliable evidence, particularly from controlled studies, shows no increase in congenital anomalies, including genital abnormalities in male or female infants, from exposure during pregnancy to progesterone or hydroxyprogesterone."*

6. ASSESSMENT OF BENEFIT/RISK AND OVERALL CONCLUSIONS

Preterm birth is the leading cause of perinatal and neonatal morbidity and mortality in the US and, as such, is well recognized as a serious public health concern. Moreover, despite both educational and medical prenatal interventions, the rate of preterm births continues to rise: 12.5% of all births are now preterm (<37 weeks gestation), compared with a rate of 9.4% in 1981.

Multiple neonatal complications are associated with preterm birth, including respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and infections resulting from immature immune systems. However, the effects of preterm birth may extend well beyond the neonatal period, with increased risks of lifelong medical, developmental, and social problems. Long-term morbidities associated with prematurity include mental retardation, retinopathy of prematurity, and cerebral palsy. As one of the most pronounced manifestations of preterm birth, the relative risk for the development of cerebral palsy is nearly 40 times that for a term infant.

Many children born prematurely "catch up" developmentally in later childhood to term-born infants. The social and emotional costs of this process, for both children and their families, are difficult to completely quantify. However, financial costs are often utilized as a surrogate measure of neonatal morbidities. In 2003, US hospitals charged an estimated $18.1 billion to treat infants with a diagnosis of prematurity or low birth weight — nearly *half* of all hospital charges for all infants in the US. On average, these preterm infants spend 16.8 days in the hospital during their first year of life compared to 2.3 days for term infants; direct costs for that first year of care are estimated to be *15 times* that for healthy term infants.

While many factors lead to an increased risk of preterm birth, a woman's previous pregnancy history is one of the most important factors. The risk of a subsequent preterm delivery is 2.5 times greater for a woman who has experienced a prior spontaneous preterm birth — an easily identifiable population that is an appropriate target for pharmacological intervention.

Based on the NICHD studies described in detail in this document, as well as the data available in the literature of earlier studies, 17P has been proven not only effective, but also safe for 2 critical populations — both mother and child — and merits approval for the following indication:

> *GESTIVA (17P) is indicated for the prevention of preterm birth in pregnant women with a history of at least 1 spontaneous preterm birth.*

Benefits of 17P

The benefits of 17P have been described at length throughout this document. The product is not only highly effective at reducing the risk of preterm birth and prolonging pregnancy, but mothers treated with it give birth to healthier neonates.

- *Prevention of Preterm Birth*

  17P has been proven effective in preventing recurrent spontaneous preterm birth in women with a singleton pregnancy. Evidence for this benefit was suggested in 6 other controlled clinical studies, published between 1964 and 1986 with varied study designs and dosing regimens, and confirmed in the well-controlled, randomized clinical study recently conducted by the NICHD at 19 study centers,

  In the NICHD study, 17P was shown to reduce the incidence of recurrent preterm birth by 32%. There were significant reductions in the rate of preterm births, regardless of definition ($<30^0$, $<32^0$, $<35^0$, or $<37^0$ weeks of gestation). Moreover, 17P was equally efficacious in women regardless of the number or gestational age of previous preterm deliveries.

- *Prolongation of Pregnancy*

  Treatment with 17P resulted in an extension of the gestational period that averaged one week across the pregnancies. Additionally, 17P treatment resulted in a shift in the distribution of gestational ages at birth, resulting in a greater percentage of infants born at term (62.9%) compared with the placebo group (45.1%). Similarly, treatment with 17P resulted in a lower percentage of infants born less than 32 weeks gestation (11.9%) compared with placebo (19.6%). Furthermore, compared with women who received placebo, women treated with 17P are less likely to give birth at each time interval from 24 weeks of gestation up to 37 weeks of gestation. This is an issue of critical importance since prolonging pregnancy by even 1 week can have profound effects on infant mortality and subsequent health.

- *Healthier Neonates*

  The shift in distribution of gestational ages at birth following treatment with 17P resulted in healthier neonates. Three important measures support this claim: Infants born to mothers treated with 17P were significantly less likely to be born at low birth weight (<2500 g), to experience serious morbidities in the neonatal period (such as NEC and IVH), or to require supplemental oxygen.

  The NICHD study also demonstrated that children born to mothers treated with 17P had fewer admissions to the NICU and, when admitted, had shorter lengths of stay. These observations were supported in a recent study by Mason and colleagues that examined 17P versus a control group on the rate of admission to the NICU, the length of stay in the NICU, and the associated costs for women treated with the drug.[73] In that study, treatment with 17P reduced the number of days spent in the NICU by 35% (149 compared with 231) and overall costs by 71% ($165,487 compared with $568,462).

Risks of 17P

In considering the risks of 17P, it has been demonstrated throughout this document that treatment with 17P is well tolerated and safe for the mother and, of importance, poses no identified risks for either fetus or child.

- *Risk for the Mother*

  17P is safe for the mother. Weekly administration of the drug was well tolerated by pregnant women, who demonstrated a very low level of discontinuations due to AEs. In fact, the most frequently reported AEs were injection site reactions that tended to be mild and short in duration, a common response to injectable products. Further, 17P treatment did not lead to increased rates of pregnancy complications or pregnancy-related procedures.

- *Risk for the Fetus and Neonate*

  There is no evidence, either from the 17P studies or the published literature, that 17P endangers the developing fetus or neonate. *In utero* exposure to 17P was safe for the developing fetus and neonate as demonstrated by comparable rates of combined miscarriages, stillbirths, and neonatal deaths between the 17P and placebo groups.

  Multiple animal and clinical studies have identified no teratogenic effects from 17-HPC. In the NICHD study, congenital anomalies occurred at similar rates in the 17P and placebo treatment groups, and these rates were consistent with overall rates in the general population. These findings were consistent with a previous analysis of *in utero* exposure to hydroxyprogesterone completed by the FDA in 1999. At that time, FDA concluded that the reliable evidence showed no increase in congenital abnormalities, including genital abnormalities, during pregnancy from exposure to hydroxyprogesterone.

  However, as a precautionary measure, 17P therapy for prevention of preterm birth is to be initiated no earlier than week 16, well into the second trimester. By avoiding treatment during critical embryonic development during the first trimester, the fetus is not exposed to 17P at the time of highest risk for development of congenital anomalies.

- *Risk for the Child*

  A follow-up safety study conducted by the NICHD examined children who had been exposed *in utero* to 17P using a broad range of developmental measures, which included information on communication, gross and fine motor skills, problem solving, and personal-social interaction and physical growth. The data from that study demonstrated that for children between 2.5 and 5.4 years of age, *in utero* exposure to 17P was not associated with developmental delays.

Multiple published studies explored the long-term medical or social effects of 17P in children up to 11 years of age and identified no evidence that *in utero* exposure to 17P posed a risk to the fetus.

In summary, 17P has been shown to be effective and safe for use in the prevention of recurrent preterm birth in singleton pregnancies. Based on the NICHD study and other published results regarding the efficacy and safety of the drug, in 2003 the American College of Obstetricians and Gynecologists Committee on Obstetric Practice recommended progesterone supplementation be used to prevent recurrent preterm birth. As a result, according to the preliminary results of a recent survey, progesterone is now being used by 67% of certified maternal-fetal medicine physicians.

The only current source for this treatment is product compounded by local pharmacies. FDA approval of 17P will ensure the availability of comprehensive labeling, which will provide standardized and accurate guidance on patient selection, dosing and administration instructions and relevant safety information. Additionally, an FDA-approved source will also ensure consistent drug quality, broader availability and a disciplined approach to safety surveillance.

17P represents an important advance for women and children who might otherwise suffer from the potentially damaging effects of preterm birth. The NICHD study demonstrates that 17P is highly effective, and that this benefit results in extended gestational periods and healthier neonates. The low numbers of at-risk women needed to treat further illustrates 17P's efficacy. Specifically, a physician would need to treat 5.6 patients to prevent 1 preterm birth $<37^0$ weeks, 11.0 patients to prevent 1 preterm birth $<35^0$, and 14.2 patients to prevent 1 preterm birth $<32^0$ weeks.

17P is also safe for the mother and her child, as it is well tolerated by the mother and does not cause congenital anomalies or developmental delays during childhood. The benefits far exceed the risks associated with its use. Given the clear unmet medical need and the highly favorable benefit/risk ratio, the case for the approval of 17P is compelling as it can result in a reduction in the number of preterm births in the United States and specifically addresses an important and unmet health care problem.

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