STUDY PROTOCOL

IND NUMBER: 68,108

A PHASE 3B, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND STUDY OF HYDROXYPROGESTERONE CAPROATE INJECTION, 250 MG/ML, VERSUS VEHICLE FOR THE PREVENTION OF PRETERM BIRTH IN WOMEN WITH A PREVIOUS SINGLETON SPONTANEOUS PRETERM DELIVERY

PROTOCOL NUMBER: 17P-ES-003

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Sponsor:	AMAG Pharma USA, Inc. 1100 Winter Street Waltham, MA 02451
Sponsor Contact/ Project Manager:	[redacted] Director Clinical Affairs AMAG Pharma USA, Inc. 1100 Winter Street Waltham, MA 02451 Telephone: [redacted] E-mail: [redacted]
Global Medical Monitor:	[redacted] Telephone: E-mail: [redacted]
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Confidentiality Statement:	The information contained in this document, especially unpublished data, is the property of the sponsor and is therefore provided to you in confidence as an investigator, potential investigator, or consultant. The information may be reviewed by you, your staff, and your Internal Review Board/Ethics Committee. It is understood that this information will not be disclosed to others without written authorization from the sponsor.
Ethics Statement:	The study will be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

SIGNATURE PAGE

PROTOCOL TITLE: A Phase 3B, Multi-Center, Randomized, Double-Blind Study of Hydroxyprogesterone Caproate Injection, 250 mg/mL, Versus Vehicle for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous Preterm Delivery

PROTOCOL NUMBER: 17P-ES-003

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PROTOCOL SUMMARY

Protocol Number:	17P-ES-003
Title:	A Phase 3B, Multi-Center, Randomized, Double-Blind Study of Hydroxyprogesterone Caproate Injection, 250 mg/mL, Versus Vehicle for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous Preterm Delivery
Study Phase:	Phase 3B
Study Sites:	Sites will be recruited in the United States and other countries.
Study Drug, Dosage and Route of Administration:	Hydroxyprogesterone Caproate Injection, 250mg/mL (17P), weekly 1 mL intramuscular injections until 36^6 weeks of gestation or delivery, whichever occurs first.
Control Drug, Dosage, and Route of Administration:	Vehicle, weekly intramuscular injections of 1 mL vehicle (castor oil, benzyl benzoate and benzyl alcohol) until 36^6 weeks of gestation or delivery, whichever occurs first.
Objectives:	There are two co-primary objectives of this study 1. Determine if treatment with 17P reduces the rate of preterm birth < 35^0 weeks of gestation in women with a previous singleton spontaneous preterm delivery. 2. Determine if 17P reduces the rate of neonatal mortality or morbidity. Neonatal mortality or morbidity is measured by a composite index comprised of: o Neonatal death. o Grade 3 or 4 intraventricular hemorrhage. o Respiratory distress syndrome. o Bronchopulmonary dysplasia. o Necrotizing enterocolitis. o Proven sepsis. The secondary objectives of this study are to: o Exclude a doubling of the risk of fetal/early infant death, defined as spontaneous abortion/miscarriage (delivery from 16^0 through 19^6 weeks of gestation) or neonatal death occurring in liveborns born at less than 24 weeks gestation or stillbirth (antepartum or intrapartum death from 20 weeks gestation through term), in the 17P group compared to the vehicle group. o Determine if 17P reduces the rate of preterm birth < 32^0 weeks of gestation. o Determine if 17P reduces the rate of preterm birth < 37^0 weeks of gestation. o Determine if 17P reduces the rate of stillbirth defined as all stillbirths/fetal deaths/in-utero fetal losses occurring from 20 weeks gestation until term. o Determine if 17P reduces the rate of neonatal death (from minutes after birth until 28 days of life) occurring in liveborns born at 24 weeks gestation or greater. o Evaluate the pharmacokinetics/pharmacodynamics (PK/PD) of 17P in a subset of pregnant women.

Subject Population:	A total of 1707 women (1138 active and 569 vehicle) with a singleton pregnancy, aged 18 years or older, with a documented history of a previous singleton spontaneous preterm delivery.
Study Design:	This study is a multi-center, randomized, double-blind, vehicle-controlled clinical trial. Subjects will be assessed and receive weekly injections of study drug from randomization (16^0 through 20^6 weeks of gestation) until 36^6 weeks of gestation or delivery, whichever occurs first.
Efficacy Assessments:	All randomized subjects will be followed until delivery for efficacy assessments. The primary and secondary maternal outcome measures will be determined based on the date of delivery and the estimated date of confinement (EDC), which is evaluated in a standardized manner. Neonates born to randomized subjects will be followed until day 28 or the date of discharge from the NICU, whichever occurs later. Discharge from the NICU is defined as discharge to any of the following: home, a non-medical facility, a chronic-care facility, or a step-down unit. The neonatal outcome measures will be determined from review of the neonatal medical record and will be based on standardized definitions of the morbidity measures.
Pharmacokinetic Assessments:	Pharmacokinetic assessments will be made based on a sparse sampling of approximately 450 subjects (300 active and 150 vehicle) stratified according to body mass index (BMI) to analyze the dose-plasma concentration-time relationship of 17P. Three blood samples will be drawn: 1. Before study drug dosing at either Visit 6 or 7 (i.e., Dose 5 or 6). 2. Before study drug dosing at either Visit 8 or 9 (i.e., Dose 7 or 8). 3. At a separate, non-dosing visit 1 to 6 days after Visit 9, 10, or 11 (i.e., 1 to 6 days after Doses 8, 9, or 10). Subjects will be stratified 2:1 (17P: vehicle) such that an even distribution of samples will be drawn on day 1, day 2, day 3, day 4, or day 5/6 post-dose. This will result in approximately 60 17P and 30 vehicle samples on each day interval. The dependence of apparent clearances and volumes on BMI will be examined as the primary covariate. Pharmacokinetic models to evaluate effects on concomitant medications that may affect the inhibition or induction of HPC will be evaluated and modeled as data permit.
Safety Assessments:	Safety assessments include but are not limited to determination of maternal adverse events, maternal pregnancy complications, and investigation of the cause of stillbirth/fetal death/in-utero fetal loss and will be based on standardized definitions. Maternal pregnancy complications include such events as gestational diabetes, oligohydramnios, significant antepartum bleeding or hemorrhage, preeclampsia, gestational hypertension, abruption, and chorioamnionitis.
Statistical Methods:	Using a 2:1 randomization, a total of 1665 live born infants are required to detect a reduction of 35% in the rate of the composite index (from 17% to 11%) with a power of 90% (assuming a two-sided type I error of 5%). Assuming 2.5% of pregnancies will result in miscarriage or stillbirth, an additional 42 women need to be enrolled for a total of 1707 women (1138 active and 569 vehicle). A total sample size of 1707 subjects provides 98% power to detect a reduction of approximately 30% in the rate of preterm birth $< 35^0$ weeks of gestation (from 30% to 21%) using a two-sided type I error of 5%. The effect size for the neonatal composite index as well as preterm birth $< 35^0$ weeks gestation was chosen to represent a clinically significant reduction. Significant differences between the 17P and vehicle group in the proportion of subjects who deliver prior to 35^0 weeks gestation will be determined using a

Cochran-Mantel-Haenszel test stratified by gestational age at randomization (16^0 weeks - 17^6 weeks gestation and 18^0 weeks – 20^6 weeks gestation), where the effective sample sizes for each treatment group and stratum will be derived from Greenwood's formula and a staggered entry Kaplan-Meier analysis using the time from randomization until delivery as the analysis variable. Subjects with missing outcome data will be censored on the date last known pregnant.

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

A two-sided 95% confidence interval (CI) for the relative risk of fetal/early infant death for 17P relative to vehicle will be calculated using the method of Cochran-Mantel-Haenszel stratified by gestational age at randomization. If the upper bound of the CI is less than or equal to 2.0, a doubling in risk of fetal/early infant death can be ruled out.

The percentage of subjects with a preterm birth $<32^0$ and $<37^0$ weeks of gestation will also be determined from the staggered entry Kaplan-Meier analysis and tested for statistical differences using the same analytic approach as for $<35^0$ weeks. Significant differences between the 17P and vehicle groups in stillbirths and neonatal deaths will be determined using the Cochran-Mantel-Haenszel test stratified by gestational age at randomization.

ABBREVIATIONS

ABBREVIATION	TERM
17P	Hydroxyprogesterone Caproate Injection, 250 mg/mL
AE	Adverse event
BMI	Body mass index
BPD	Bronchopulmonary dysplasia
BV	Bacterial vaginosis
CFR	Code of Federal Regulations
CI	Confidence interval
CV	Curriculum vitae
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
EDC	Estimated date of confinement
FDA	Food and Drug Administration
GCP	Good Clinical Practice Guidelines
HELLP	Hemolytic anemia elevated liver enzymes and low platelet count
HPC	Hydroxyprogesterone caproate
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
ITT	Intent-to-treat
IVH	Intraventricular hemorrhage
IVRS	Interactive voice response system
LMP	Last menstrual period
MedDRA®	Medical Dictionary for Regulatory Activities
MITT	Modified intent to treat
NEC	Necrotizing enterocolitis
NDA	New Drug Application
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
NONMEM	Nonlinear mixed effects modeling
OTC	Over-the-counter
PD	Pharmacodynamic
PDA	Patent ductus arteriosus
PE	Physical examination

ABBREVIATION	TERM
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
POME	Pulmonary oil microemboli
PP	Per-protocol population
pPROM	Preterm premature rupture of membranes
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SAE	Serious adverse event
TEAE	Treatment emergent adverse events
US	United States

1 INTRODUCTION

1.1 Prevalence and Prevention of Preterm Birth

Preterm birth, defined as birth before the 37th week of gestation, is a very serious health concern, and is recognized as the leading cause of neonatal mortality and morbidity in the US.[1] Despite advances in perinatal care, the incidence of preterm birth remains high in the US. According to the Centers for Disease Control and Prevention, it peaked in 2006 when 12.8% of the 4.3 million births occurred preterm, which represented a 21% increase since 1990 and a 33% increase from 1981 to 2004.[2,3] Since 2006, the rate has fallen slightly to a rate of 11.99% in 2010.[4] At its current rate, 1 preterm birth occurs nearly every minute in the US.

One of the most significant risk factors for preterm birth is previous pregnancy history. 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] Prophylactic methods for prevention of preterm birth, including tocolytic drugs, bed rest, and other interventions such as cerclage, have been shown in most studies to be ineffective.[7,8] One of the preventive measures that has shown effectiveness in randomized trials is the use of progesterone agents.[9,10] Progesterone has been shown to support gestation and to inhibit uterine activity.

Hydroxyprogesterone caproate (HPC) has a long history of use in pregnant women dating back numerous decades when it was marketed as Delalutin® (E.R. Squibb & Sons, Inc.) for habitual and recurrent abortion, threatened abortion, and post-partum after pains. In addition a number of studies support the use of HPC for prevention of preterm births.[11-15]

1.2 Hydroxyprogesterone Caproate (HPC)

In a large, controlled clinical study conducted by the National Institute of Child Health and Human Development (NICHD), 17P was shown to significantly reduce the rate of recurrent preterm birth among women at high-risk for preterm birth.[15] This multi-center, randomized, double-blind, placebo-controlled study enrolled a high-risk population of pregnant women between 16^0 and 20^6 weeks of gestation with a history of previous singleton spontaneous preterm delivery. A total of 463 subjects were randomized in a 2:1 ratio to receive weekly injections of either 17P (310 subjects) or placebo (153 subjects) through 36^6 weeks of gestation or delivery, whichever occurred first.

The results from this study confirmed earlier reports of the efficacy of HPC in preventing preterm birth. Treatment with 17P significantly reduced the incidence of preterm birth less than 37^0 weeks of gestation compared with placebo ($P < 0.001$). The 17P treatment also significantly reduced the incidence of preterm births when defined as $< 35^0$ ($P = 0.0263$) or $< 32^0$ ($P = 0.0273$) weeks of gestation and prolonged the duration of pregnancy from time of enrollment ($P = 0.0024$).

Treatment with 17P also led to significantly ($P < 0.05$) lower rates of low birth weight infants (< 2500 g), neonates with necrotizing enterocolitis (NEC), neonates having any grade 3 or 4 intraventricular hemorrhage (IVH), neonates requiring supplemental oxygen, and neonates requiring admission to the neonatal intensive care unit (NICU). Although the differences did

not reach statistical significance, rates of respiratory distress syndrome (RDS), ventilator support, and patent ductus arteriosus (PDA) were also reduced following 17P treatment.

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). Treatment with 17P did not lead to increased rates of pregnancy complications or pregnancy-related procedures. The most common pregnancy complications (those reported by > 5% of subjects) were preeclampsia or gestational hypertension and gestational diabetes, which occurred at comparable rates in the 17P and placebo groups. The total incidence of miscarriages, stillbirths, and neonatal deaths during the study was not different between the 2 treatment groups: 6.2% in the 17P group and 7.2% in the placebo group ($P = 0.6887$). The incidence of miscarriages and stillbirths was slightly higher in the 17P group (3.5% vs. 1.3%); while the incidence of neonatal deaths was 2-fold lower in the 17P group (2.7% vs. 6.0%). Neither of these between-group differences was statistically significant. Moreover, the rates of congenital anomalies identified at birth in the NICHD study were similar between treatment groups and were consistent with those reported in general population surveys.

In the follow-up study of children born to mothers who participated in the NICHD 17P study, the authors reported that they did not detect differences in developmental delays, safety concerns related to overall health or physical development, or genital or reproductive anomalies between children with in-utero exposure to placebo and in-utero exposure to 17P.

The results of the NICHD 17P study 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.[15,16-18]

1.3 Rationale for Clinical Trial

The FDA-approved indication for 17P (Makena, Hydroxyprogesterone Caproate Injection) states that it is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. However, since this is a subpart-H approval the following caveat is added: "The effectiveness of Hydroxyprogesterone Caproate Injection is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity."

Study 17P-ES-003 is a multi-center, randomized, double-blind, vehicle-controlled clinical trial of 17P designed to have sufficient size and power to evaluate both a reduction in the risk of preterm birth < 35^0 weeks of gestation and an improvement in neonatal mortality and morbidity if one exists. The study will include women with a singleton pregnancy, aged 18 years or older, with a previous singleton spontaneous preterm delivery, and includes a population pharmacokinetic (PK) substudy to assess the HPC exposure-response relationship and the effect of BMI on the PK of 17P. The effects of concomitant medications on 17P pharmacodynamics will also be investigated.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The two co-primary objectives of this study are to:

- Determine if treatment with 17P reduces the rate of preterm birth < 35^0 weeks of gestation in women with a singleton pregnancy, aged 18 years or older, with a previous singleton spontaneous preterm delivery.
- Determine if 17P reduces the rate of neonatal mortality or morbidity. Neonatal mortality or morbidity is measured by a composite index comprised of (See Section 13.2 for definitions):
  - Neonatal death.
  - Grade 3 or 4 intraventricular hemorrhage.
  - Respiratory distress syndrome.
  - Bronchopulmonary dysplasia.
  - Necrotizing enterocolitis.
  - Proven sepsis.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Exclude a doubling of the risk of fetal/early infant death, defined as spontaneous abortion/miscarriage (delivery from 16^0 through 19^6 weeks of gestation) or neonatal death occurring in liveborns born at less than 24 weeks gestation or stillbirth (antepartum or intrapartum death from 20 weeks gestation through term), in the 17P group compared to the vehicle group.
- Determine if 17P reduces the rate of preterm birth < 32^0 weeks of gestation.
- Determine if 17P reduces the rate of preterm birth < 37^0 weeks of gestation.
- Determine if 17P reduces the rate of stillbirth defined as all stillbirths/fetal deaths/in-utero fetal losses occurring from 20 weeks gestation until term.
- Determine if 17P reduces the rate of neonatal death (from minutes after birth until 28 days of life) occurring in liveborns born at 24 weeks gestation or greater.
- Evaluate the PK/PD of 17P in a subset of pregnant women.

3 STUDY PLAN

3.1 Overall Design

This study is a multi-center, randomized, double-blind, vehicle-controlled clinical trial in women with a singleton pregnancy, aged 18 years or older, with a history of a previous singleton spontaneous preterm delivery. A total of 1707 subjects will be randomized in a

2:1 ratio to receive either 17P or vehicle, respectively. Subjects will receive weekly injections of study drug from randomization (16^0 through 20^6 weeks of gestation) until 36^6 weeks of gestation or delivery, whichever occurs first. Pharmacokinetic assessments will be made based on a sparse sampling of approximately 450 subjects (300 active and 150 vehicle), stratified according to BMI to analyze the dose-plasma concentration-time relationship of 17P. Randomized subjects will be followed for efficacy outcomes through the date of delivery and for adverse events up to the End of Treatment Period Visit defined as 35 ± 7 days after the last dose of study drug. If the End of Treatment Period Visit is prior to the date of delivery, maternal and fetal deaths should be reported until delivery. Neonates of randomized subjects will be followed until day 28 or the date of discharge from the NICU or equivalent, whichever occurs later. Discharge from the NICU is defined as discharge to any of the following: home, a non-medical facility, a chronic-care facility, or a step-down unit. At centers participating in the 17P-FU-004 study, every effort will be made to obtain informed consent for the 17P-FU-004 study from all randomized subjects while they are pregnant. If it is not possible to obtain consent during the pregnancy, consent may be obtained up to the point that their child reaches one year of age.

Table 1 provides the schedule of events for the study.

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

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

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

[c] Neonates born to randomized subjects will be followed through 28 days of life or discharge from the NICU whichever is later. Therefore, the status of all neonates (alive or dead), regardless of when they are delivered and discharged from the hospital will be obtained at least 28 days after delivery (this contact may occur at later than 28 days after delivery as long as the status of the infant on Day 28 after delivery is determined). If the neonate has been discharged from the birth hospitalization, the subject may be contacted by telephone to obtain the neonate's status. If the infant is still in the NICU or equivalent 28 days after delivery, then their status (alive or dead) will be determined upon discharge from the NICU or equivalent. This status may be obtained after the infant is discharged as long as the status of the infant on the day of discharge is determined.

[d] All randomized subjects, regardless of when they deliver, should be contacted for an End of Treatment Period Visit to obtain AE information including medications to treat AE(s). The contact can be either in person or by telephone and should occur 35 ± 7 days after the last dose of study drug.

[e] To be completed before performing any baseline procedures. Informed consent may be obtained at a gestational age of 10 weeks or greater to facilitate obtaining records from the qualifying delivery. At centers participating in the 17P-FU-004 study, every effort will be made to obtain informed consent for the 17P-FU-004 study from all randomized subjects while they are pregnant. If it is not possible to obtain consent during the pregnancy, consent may be obtained up to the point that their child reaches one year of age.

[f] Must be signed by subject in order to obtain medical records of previous deliveries.

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

[h] Conduct a brief physical examination including a brief head-to-toe visual inspection at either Baseline (Visit 1) or Visit 2 only.

[i] Prior medications include all medications taken since the start of this pregnancy, defined as 40 weeks before the project EDC and before the study drug is randomly assigned. Prior medications collection ends at Visit 2.

[j] Concomitant medications must be recorded in the electronic case report form through the End of Treatment Period Visit.

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

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

[m] Subjects will receive one injection for each week they are pregnant from randomization through 36^6 weeks gestation or delivery, whichever occurs first. As much as possible injections should be given on the same day each week. However, if a schedule change is required, in general injections should be at least 5 days apart and no more than 10 days apart.

[n] AEs are recorded from administration of the trial injection through the End of Treatment Period Visit including medications to treat the AE. Preterm birth is an anticipated outcome and is not considered an AE. Maternal or fetal deaths will be recorded through delivery.

3.2 Efficacy Assessments

All randomized subjects will be followed until delivery for efficacy assessments. The primary and secondary maternal outcome measures will be determined based on the date of delivery and the estimated date of confinement (EDC), which is evaluated in a standardized manner. Neonates born to randomized subjects will be followed until day 28 or the date of discharge from the NICU, whichever occurs later. Discharge from the NICU is defined as discharge to any of the following: home, a non-medical facility, a chronic-care facility, or a step-down unit. The neonatal outcome measures will be determined from review of the neonatal medical record and will be based on standardized definitions of the morbidity measures.

3.3 Pharmacokinetic Assessments

Subjects may be offered the opportunity to participate in a pharmacokinetic sub-study until approximately 450 subjects (300 active and 150 vehicle) have been enrolled. Pharmacokinetic assessments will be made based on a sparse sampling stratified according to pre-pregnancy BMI to analyze the dose-plasma concentration-time relationship of HPC.

Three blood samples will be drawn:

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

Study sites should follow the procedure outlined in the study manual.

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

3.4 Safety Assessments

Safety assessments include determination of maternal AE(s) and maternal pregnancy complications. Maternal pregnancy complications include, but are not limited to, the following:

- Gestational diabetes
- Oligohydramnios
- Significant antepartum bleeding or hemorrhage
- Preeclampsia
- Eclampsia
- HELLP syndrome
- Gestational hypertension
- Abruption
- Chorioamnionitis

Definitions of these maternal pregnancy complications are given in Section 13.1.

3.5 Primary and Secondary Outcomes

3.5.1 Primary Outcomes

There are two co-primary outcomes:

- Preterm birth prior to 35^0 weeks of gestation (as determined by project gestational age). All deliveries occurring from randomization until 35^0 weeks of gestation, including miscarriages occurring from 16^0 through 19^6 weeks of gestation and elective abortions, will be included.
- Composite neonatal morbidity and mortality index. The composite index includes the following:
  - Neonatal death
  - Grade 3 or 4 IVH
  - RDS
  - BPD
  - NEC
  - Proven sepsis

  Definitions of neonatal outcomes are given in Section 13.2.

3.5.2 Secondary Outcomes

The secondary outcomes include:

- Fetal/early infant death. Spontaneous abortion/miscarriage (delivery from 16^0 through 19^6 weeks of gestation) or neonatal death occurring in liveborns born at less than 24 weeks gestation or stillbirth (antepartum or intrapartum death) from 20 weeks gestation through term.
- Preterm birth prior to 32^0 weeks of gestation (as determined by project gestational age). All deliveries occurring from randomization until 32^0 weeks of gestation, including miscarriages occurring from 16^0 through 19^6 weeks of gestation and elective abortions, will be included.
- Preterm birth prior to 37^0 weeks of gestation (as determined by project gestational age). All deliveries occurring from randomization until 37^0 weeks of gestation, including miscarriages occurring from 16^0 through 19^6 weeks of gestation and elective abortions, will be included.
- Stillbirth: All stillbirths/fetal deaths/in-utero fetal losses occurring from 20 weeks gestation until term.
- Neonatal death (from minutes after birth until 28 days of life) occurring in liveborns born at 24 weeks gestation or greater.
- Dose-plasma concentration-time data of HPC analyzed using a nonlinear mixed effects modeling (NONMEM) of a population approach and the NONMEM software [redacted] The dependence of apparent clearances and volumes on BMI examined as the primary covariate through its formal inclusion in the NONMEM models.
- Pharmacokinetic models to evaluate effects on concomitant medications that may affect the inhibition or induction of HPC will be evaluated and modeled as data permit.

3.5.3 Additional Outcomes

Additional maternal outcomes that will be measured include:

- Spontaneous preterm birth prior to 37^0 and prior to 35^0 weeks of gestation. Spontaneous delivery is defined as following preterm premature rupture of membranes (pPROM) or spontaneous labor from 20^0-37^0 and 20^0-35^0 weeks of gestation or miscarriage from 16^0 through 19^6 weeks of gestation.
- Indicated preterm birth prior to 37^0 weeks of gestation. Elective abortions will be defined as indicated preterm births.
- Gestational age at delivery as determined by project gestational age.
- Miscarriage (delivery from 16^0 through 19^6 weeks of gestation).

Additional neonatal outcomes that will be measured include (See Section 13.2 for definitions):

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

4 STUDY TREATMENTS

4.1 Study Drug

4.1.1 Dosage and Administration

The study drug is 250 mg /mL of 17P given by the study site personnel as a 1 mL intramuscular injection (or 1 mL of vehicle (castor oil, benzyl benzoate and benzyl alcohol)) in the upper outer quadrant of the gluteus maximus. Slow injection (over one minute or longer) is recommended. The study drug will be dispensed by authorized site personnel and stored as multiple-dose vials containing 17P or vehicle. If required by institutional policy or the medical condition of the subject the injection may be given at an alternative location in the same muscle. Do not use product 5 weeks or more after first use. Vials and packaging should be handled according to protocol instruction.

4.1.2 Study Drug Discontinuation

The study drug should be discontinued if any of the following events occur:

- Arterial or deep venous thrombotic or thromboembolic event
- Recurrent clinical depression in subjects with a history of clinical depression

Subjects should be carefully monitored and the risk/benefit of continuing the drug should be evaluated if any of the following events occur

- Allergic reactions including urticaria, pruritis and angioedema
- Jaundice
- Hypertension

4.2 Prior/Concomitant Medications and Restrictions

4.2.1 Prior Medications

Prior medications, defined as all medications taken since the start of this pregnancy, defined as 40 weeks before the project EDC and before study drug is randomly assigned, will be recorded in the subject's electronic case report form (eCRF) at Baseline (Visit 1), and Randomization Visit (Visit 2). This will include all prescription drugs, herbal products, vitamins (including prenatal vitamins), minerals, and other over-the-counter (OTC) medications.

4.2.2 Concomitant Medications

All concomitant medications will be recorded in the subject's eCRF from the time the subject is randomly assigned at Visit 2 through the End of Treatment Period Visit. This will include all prescription drugs, herbal products, vitamins (including prenatal vitamins), minerals, and OTC medications. Any changes in concomitant medications will also be recorded in the subject's eCRF.

Since hydroxyprogesterone caproate caused acceleration of the metabolic reactions catalyzed by CYP2A6, 2B6 and 1A2, a list of medicines using these metabolic pathways is included in Section 14.

During the current pregnancy, a subject may have received an oral or intravaginal progestin other than hydroxyprogesterone caproate providing it is stopped at least 4 weeks prior to starting study medication. Any other concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator.

4.2.3 Restrictions

No attempt will be made to alter or mandate clinical management of the subjects. However, the use of other prophylactic tocolytic drugs is discouraged. If complications of the pregnancy arise, such as the following:

- Need for a cervical cerclage, or
- Fetal anomaly or trisomy, or
- Hospitalization for any reason including preterm labor,

continuation of treatment will be at the discretion of the clinician managing the subject. These complications are not necessarily indications for stopping treatment. Thus, if a subject is

hospitalized, administration of the study drug should continue during hospitalization, if possible, as well as following discharge.

4.3 Measurement of Subject Compliance and Tolerability

Subjects' ability to comply with the study protocol and procedures will be assessed at Baseline (Visit 1). The subject will receive an injection (referred to as the trial injection) of the vehicle (1 mL of castor oil, benzyl benzoate and benzyl alcohol). The subject will be told that this injection does not contain the active drug but is a test for compliance with the treatment regimen and for any unusual reactions to the injection. Subjects may return 3 or more days after the trial injection as long as randomization occurs from 16^0 through 20^6 weeks of gestation. If a subject can only receive the trial injection at a gestational age of 20^4 – 20^5 weeks and an ultrasound to screen for congenital anomalies was performed at or prior to a gestational age of 20^3 weeks, the patient may be randomized 24 hours or more following the trial injection provided that gestational age is <=20^6 weeks and in the opinion of the investigator the patient is experiencing no adverse reactions to the trial injection that would preclude their participation in the trial.

Overall subject compliance with study treatment will be assessed by determining the proportion of expected injections actually received. The date of each injection will be recorded in the subject's eCRF.

4.4 Study Drug Description

The following drug supplies will be used in the study:

Product	Supplied as:
17P	250 mg/mL HPC in multidose vials
Vehicle	Castor oil, benzyl benzoate and benzyl alcohol in multidose vials

The 17P drug product will be supplied as a sterile solution containing HPC 250 mg/mL, benzyl benzoate, castor oil, and benzyl alcohol.

Vehicle will be supplied as a sterile solution containing benzyl benzoate, castor oil, and benzyl alcohol and is matched in color and appearance compared with 17P.

4.5 Study Drug Packaging and Storage

The 17P and matching vehicle are contained in glass vials individually packaged in a cardboard box and shipped. Each vial will contain a sufficient volume to be able to withdraw five 1-mL doses.

Vials of study drug will be stored at room temperature, between 59-86ºF (15-30ºC), away from light. Store vial in the vial carton provided. Store vial upright.

4.6 Study Medication Accountability

Study sites will receive instructions on accounting for receipt of study medication, storing subject's empty vials and vials containing unused medication, and returning study medication. The investigator will maintain accurate records of receipt, return or destruction of all study medication, including the dates of receipt and return. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each subject in the study, including the number of unused doses remaining in an open multidose vial. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled and retained or destroyed according to applicable local and national regulations.

4.7 Retention of Testing Samples

Pharmacokinetic assessments will be made on three blood samples collected from the PK Population. At the request of the Food and Drug Administration (FDA), a separate aliquot of each PK blood sample will be retained for potential future analysis of any important metabolites that may be identified through ongoing PK analyses, outside of this study.

5 SUBJECT ENROLLMENT

Approximately 1707 subjects will be enrolled and randomized at approximately 90 sites. Sites will be recruited in the United States and other countries.

A subject is considered enrolled in the study if she receives the trial injection. Each subject will be assigned to a randomized study treatment only if she meets all of the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study:

1. Age ≥ 18 years.
2. Singleton gestation.
3. Project gestational age 16^0 weeks of gestation or more and less than or equal to 20^6 weeks of gestation at the time of randomization, based on clinical information and evaluation of the first ultrasound, as described in "Gestational Age Determination" below.
4. Documented history of a previous singleton spontaneous preterm delivery. Spontaneous preterm birth is defined as delivery from 20^0 to 36^6 weeks of gestation following spontaneous preterm labor or pPROM. Where possible, the gestational age of the previous preterm birth (referred to as the qualifying delivery) should be determined as described in "Gestational Age Determination" below. If the gestational age at delivery is obtained directly from the medical record and more than one gestational age appears, the latest will be used. As a validation of the gestational age of the previous delivery, if the infant weighed more than 3300 grams[19] (the birth weight 90th percentile for 36 weeks gestational age), this

will not qualify as preterm. The previous preterm delivery cannot be an antepartum stillbirth.

5.1.1 Gestational Age Determination

Gestational age is determined in the following manner and is denoted 'project gestational age'. The 'project EDC' will be determined by the combination of a reliable menstrual history and measurements obtained at the subject's first ultrasound examination. The project EDC is based on the project gestational age and cannot be revised once a determination has been made. Because the project EDC depends on information from the earliest dating ultrasound, if no ultrasound has been performed previously, one must be performed before the subject can be randomized.

1. The first day of the last menstrual period (LMP) is determined and a judgment made as to whether or not the subject has a 'sure' LMP date.
2. If the LMP date is unsure, the ultrasound measurements obtained at the subject's first ultrasound examination will be used to determine the project gestational age, by the standard method of ultrasound gestational age determination at that institution.
3. If the date of her LMP is sure, and the ultrasound confirms this gestational age within the number of days specified in 'Cut-offs for Using LMP to Determine Gestational Age' (Table 2), the LMP derived gestational age will be used to determine the project gestational age.
4. If the ultrasound-determined gestational age does not confirm the LMP generated gestational age within the number of days specified in *Table 2* below, the ultrasound is used to determine the project gestational age.

Table 2 Cut-offs for Using LMP to Determine Gestational Age

Gestational age at first ultrasound by LMP	Ultrasound agreement with LMP
Up through 19^6 weeks of gestation	±7 days
20^0 through 20^6 weeks of gestation	±14 days

5.2 Exclusion Criteria

1. Multifetal gestation.
2. Known major fetal anomaly or fetal demise. An ultrasound examination between 14^0 through 20^3 weeks of gestation must be performed to rule out fetal anomalies.
3. Subjects who have received a progestin during the current pregnancy AND meet one of the following criteria are excluded.
    3.1. The progestin was administered in the 4 weeks preceding the first dose of study medication
    3.2. Subjects received hydroxyprogesterone caproate
    3.3. The progestin was administered by a route other than oral or intra-vaginal.

4. Heparin therapy during current pregnancy or history of thromboembolic disease.
5. Maternal medical/obstetrical complications including:
   - Current or planned cerclage
   - Hypertension requiring medication
   - Seizure disorder
6. Subjects with a uterine anomaly (uterine didelphys or bicornuate uterus). However, subjects with uterine fibroids are eligible for the study.
7. Unwillingness to comply with and complete the study.
8. A 14^0 through 20^3 weeks of gestation ultrasound cannot be arranged before randomization.
9. Participation in an antenatal study in which the clinical status or intervention may influence gestational age at delivery.
10. Participation in this trial in a previous pregnancy. Women who were screened in a previous pregnancy, but not randomized, do not have to be excluded.
11. Known hypersensitivity to hydroxyprogesterone caproate injection or its components.
12. Have any significant medical disorder that, in the opinion of the investigator, would be a contraindication to the use of the drug including the following list from section 5.3.2 of the investigational brochure:
    - Current or history of thrombosis or thromboembolic disorders
    - Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
    - Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
    - Cholestatic jaundice of pregnancy
    - Liver tumors, benign or malignant, or active liver disease
    - Uncontrolled hypertension

    Other examples to consider include uncontrolled diabetes, known HIV infection or renal dysfunction.
13. Have any significant medical disorder that, in the opinion of the investigator, would preclude accurate evaluation of the subject's condition or outcome or compromise the subject's safety in the study.

5.3 Randomization Procedures

Subjects will be randomly assigned in a 2:1 ratio to 17P or vehicle treatment (two 17P to 1 vehicle subject) using a blocked randomization sequence stratified by study site and gestational age randomization (16^0 weeks - 17^6 weeks gestation and 18^0 weeks – 20^6 weeks gestation). Randomization is stratified by study site to ensure balance between the 2 treatment groups with respect to anticipated differences in the clinic population and possible site-to-site differences in subject management. The rationale for 2:1 randomization is that since the study involves weekly injections, subjects may be more willing to participate if they know that they have a 2 to 1 chance of receiving active medication. Randomization occurs when a randomization number has been assigned to a subject.

If a subject does not attend her randomization visit, the investigator should attempt to contact the subject and reschedule the randomization visit. If the coordinator cannot contact the subject or the randomization visit cannot be rescheduled ≤ 20^6 weeks of gestation, the subject cannot be randomized. Randomization will occur through the use of an interactive voice response system (IVRS).

5.4 Blinding Procedures

This will be a double-blind study. The subjects, clinical site staff, and sponsor will not be aware of the treatment assignment. A Data and Safety Monitoring Board (DSMB) will review summary safety data (see Section 9.6.1) and the DSMB Charter will provide the option for the DSMB to request unblinded review of the data.

5.5 Breaking the Blind

With the exception of the DSMB data review, the study blind will not be broken until all subjects have completed the study and the database is locked. Upon request, the subject will be advised of her treatment assignment after her infant has completed the follow-up study, if applicable. Only in the case of an emergency, when knowledge of the study drug is essential for the immediate clinical management or welfare of a specific subject, may the investigator unblind a subject's treatment assignment.

Prior to any unblinding, the investigator is strongly advised to discuss options with the Medical Monitor or appropriate sponsor study personnel. As soon as possible, and without revealing the subject's study treatment assignment (unless important to the safety of subjects remaining in the study), the investigator must notify the sponsor if the blind is broken for any reason and the investigator was unable to contact the sponsor prior to unblinding. The investigator will record in source documentation the date and reason for revealing the blinded treatment assignment for that subject.

5.6 Subject Withdrawal

Subjects may prematurely discontinue study drug or withdraw consent to participate in this study at any time without penalty or loss of benefits to which the subjects are otherwise entitled.

5.6.1 Subject Withdrawal from Study Drug

Subjects will be considered withdrawn from study drug if they are prematurely discontinued from administration of study drug (i.e., prior to the anticipated full course of study drug therapy for a reason other than delivery). If possible the subject should remain on study and at a minimum, delivery data will be obtained. Reasons for subject withdrawal from study drug are recorded in the appropriate page(s) of the eCRF and may include, but are not limited to:

- Withdrawal of consent.
- At request of the investigator due to the occurrence of an AE that, in the opinion of the investigator, warrants the subject's permanent discontinuation from study drug therapy. In

the event of discontinuation from study drug therapy due to the occurrence of an AE, the study site should notify the Medical Monitor as soon as possible (see Section 8.6). At the time of withdrawal, the site staff should attempt to obtain end-of-study information from the subject.

- Significant subject noncompliance, defined as unwillingness or inability to adhere to the prescribed dosing regimen.

5.6.2 Subject Withdrawal from Study

A subject is considered withdrawn from the study if the subject delivery data are not obtained (i.e., the subject is lost to follow-up). The investigator should make reasonable attempts to contact the subject including at least 2 phone calls followed by a registered letter, receipt requested. If the subject is determined to be lost to follow-up, the last known date pregnant should be recorded in the appropriate page of the eCRF.

5.6.3 Replacements

Randomized subjects who are withdrawn from the study or lost to follow-up will not be replaced.

5.6.4 Sponsor's Termination of Study

The sponsor reserves the right to terminate an investigational site or this clinical study at any time. Reasons for termination may include, but are not limited to, the following:

- The incidence or severity of AEs in this study indicates a potential health hazard to subjects.
- Serious or persistent noncompliance by the investigator with the protocol, clinical research agreement, US FDA Form FDA 1572, GCP, or other applicable regulatory guidelines in conducting the study.
- IRB/IEC decision to terminate or suspend approval for the investigation or the investigator.
- Investigator request to withdraw from participation.
- Subject enrollment is unsatisfactory.

6 STUDY VISITS

Each subject will be seen for weekly study visits to administer intramuscular injections of study drug. Subjects will receive one injection for each week they are pregnant from randomization through 36^6 weeks gestation or delivery, whichever occurs first. As much as possible, injections should be given on the same day each week. However, if a schedule change is required, in general injections should be at least 5 days apart and no more than 10 days apart.

Three blood samples will be collected from approximately 450 subjects (300 active and 150 vehicle) for the population PK analysis at specified visits during the trial. If the treatment is

interrupted for any reason, the subject will be encouraged to resume treatment with their study drug and continue until 36^6 weeks of gestation or delivery, whichever occurs first.

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

6.1 Baseline (Visit 1)

The Baseline (Visit 1) will occur wherever possible within 7 days before randomization and administration of study medication. Prior to performing baseline procedures, each potential subject (or legal guardian of the potential subject) will sign an informed consent form (ICF). All subjects who present for prenatal care after 15^0 weeks of gestation and before 20^3 weeks gestational age are eligible for screening. The latest gestational age for randomization is 20^6 weeks of gestation.

The potential subject/legal guardian will be asked to sign a medical records release so that the medical records of her previous delivery(ies) may be obtained. Documentation of the subject's previous delivery(ies) will be reviewed to ensure the subject meets the inclusion criteria. If an abdominal ultrasound examination has not been performed at 14^0 through 20^3 weeks of gestation, one must be arranged prior to randomization. The results of the ultrasound must also be reviewed to check for exclusion criteria and, if it is the subject's first ultrasound, gestational age. The ultrasound results will be made available to the subject's physician.

At Baseline (Visit 1), potential subjects will undergo the following procedures:

- If not already done, obtain written informed consent. No study specific procedures will be performed without informed consent. Informed consent may be obtained at a gestational age of 10 weeks or greater to facilitate obtaining records from the qualifying delivery.
- At centers participating in the 17P-FU-004 study, every effort will be made to obtain informed consent for the 17P-FU-004 study from all randomized subjects while they are pregnant. If it is not possible to obtain consent during the pregnancy, consent may be obtained up to the point that their child reaches one year of age.
- If not already done, obtain permission to release medical records from previous preterm birth.
- Obtain demographic information including age, ethnicity, and race.
- Obtain social history including marital status, years of education, alcohol use, tobacco use, and illicit drug use.
- Obtain medical and obstetrics history, including pre-pregnancy weight, history of significant illnesses, previous surgical history, sexually transmitted disease history, history of douching before and during pregnancy, history of uterine and vaginal infection, history of corticosteroid use, outcome of all prior pregnancies, potential risk factors for miscarriage.

- Collect prior medications information, including all medications taken at any time since the start of this pregnancy, defined as 40 weeks before the project EDC, through the current date.
- Obtain height.
- Obtain weight.
- Determine the project gestational age and EDC if an ultrasound has been completed.
- A brief physical examination including a brief head-to-toe visual inspection must be conducted at either Baseline (Visit 1) or Visit 2.
- Receive the trial injection.
- Monitor for and record presence or absence of pulmonary oil microemboli (POME) symptoms, such as transient coughing or dyspnea, that may occur within the first 10 minutes after administration of the injection (please refer to Section 8.1 – Adverse Events).
- Record AE(s) associated with the trial injection.
- Record information related to risk factors of miscarriage.
- If one has not been conducted, schedule an ultrasound.
- Schedule randomization (Visit 2).

6.2 Active Treatment Period (Visit 2 to 36^6 Weeks of Gestation or Delivery)

During the Active Treatment Period, subjects will report to the site weekly until the subject is 36^6 weeks of gestation or delivers, whichever occurs first.

At Active Treatment Period Visits, subjects will undergo the following procedures:

- Review medications and record as concomitant medications on the subject's eCRF.
- At visit 2, confirm the subject still meets the inclusion and exclusion criteria, randomize the subject and record any new AE(s) associated with administration of the trial injection.
- At visit 2, conduct a brief physical examination including a brief head-to-toe visual inspection, if not conducted at Baseline (Visit 1).
- Obtain weight.
- Administer intramuscular injection of study drug.
- Adverse events will be collected at all study visits that occur after the subject's randomization and administration of the initial dose of study medication.
- Monitor for and record presence or absence of POME symptoms, such as transient coughing or dyspnea, that may occur within the first 10 minutes after administration of the injection (please refer to Section 8.1 – Adverse Events).
- Record any pregnancy complications, including complications associated with fetal/early infant death, visits for labor and delivery or hospitalization(s) for preterm labor.
- For subjects in the PK substudy, collect a blood sample for PK analysis as appropriate:

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

6.3 Delivery and Hospitalization

As soon as possible after discharge from delivery hospitalization, subjects will undergo the following procedures:

- Review concomitant medications if prior to End of Treatment Period Visit.
- Record any pregnancy complications, including complications associated with fetal/early infant death.
- Record the date of hospital admission and discharge.
- Record delivery data including the date and time of labor onset, membrane rupture, delivery, and delivery route.
- Record neonatal baseline data.
- Record AE(s) if prior to End of Treatment Period Visit.

6.4 Neonatal Hospitalization

All live births who are admitted to the NICU (NICU level 2-3 or equivalent, specialty or sub-specialty care)[20], who experienced one of the morbidities in the neonatal index or who died will undergo the following procedures:

- Record neonate's clinical data including composite index measures (See Section 13.2 for definitions).
- If applicable, record hospital transfer information.
- If applicable, collect autopsy information on neonatal death.

6.5 Neonate Follow-Up

Neonates born to randomized subjects will be followed through 28 days of life or discharge from the NICU whichever is later. Therefore, the status of all neonates (alive or dead), regardless of when they are delivered and discharged from the hospital will be obtained at least 28 days after delivery (this contact may occur at later than 28 days after delivery as long as the status of the infant on Day 28 after delivery is determined). If the neonate has been discharged from the birth hospitalization, the subject may be contacted by telephone to obtain the neonate's status. If the infant is still in the NICU or equivalent 28 days after delivery, then their status (alive or dead) will be determined upon discharge from the NICU or equivalent.

This status may be obtained after the infant is discharged as long as the status of the infant on the day of discharge is determined.

6.6 End of Treatment Period Visit

All randomized subjects, regardless of when they deliver, should be contacted for an End of Treatment Period Visit to collect concomitant medications and AE information including medications to treat AE(s). The contact can be either in person or by telephone and should occur 35 ± 7 days after the last dose of study drug.

At the End of Treatment Period Visit, subjects will undergo the following procedures:

- Record AE(s).
- Review concomitant medications and medications used to treat AE(s).

6.7 Early Withdrawal Procedures

If a subject prematurely discontinues study medication she will be asked about her reason for discontinuation of study drug. The subject will remain in the study and maternal or fetal deaths, delivery and neonatal data will be obtained. If a subject prematurely discontinues study medication and is no longer making regular visits to the study site, every attempt will be made to obtain the last known date that she was pregnant from clinic records, emergency room records, labor and delivery visits, or records from other hospitals. If the subject is permanently lost to follow-up a brief explanation will be documented.

7 STUDY ASSESSMENTS

7.1 Demographic Data/Medical and Obstetrical History

Demographic data and a complete medical/obstetrical history including information related to additional risk factors of miscarriage will be collected at Baseline (Visit 1).

7.2 Physical Examination

A brief physical examination including visual inspection of the subject's anterior and posterior torso and extremities will be conducted at either Baseline (Visit 1) or Visit 2.

7.3 Height and Weight Measurements

The subject's height and pre-pregnancy weight will be recorded at Baseline (Visit 1) only. The subject's weight will be recorded at each study visit from Baseline through the last dose of study drug.

7.4 Prior and Concomitant Medication

Prior medications, defined as all medications taken during pregnancy from the start of this pregnancy, defined as 40 weeks before the project EDC, until study drug is randomly assigned

will be recorded at Baseline and Randomization visits. Concomitant medications will be recorded at each study visit after the subject is randomized (Visit 2) through the End of Treatment Period Visit.

7.5 Ultrasound

All subjects must have an ultrasound at 14^0 through 20^3 weeks of gestation to rule out fetal anomalies. If one has not been done as part of standard prenatal care, one must be completed prior to randomization.

7.6 Pharmacokinetic Testing

Pharmacokinetic assessments will be made based on a sparse sampling of approximately 450 subjects (300 active and 150 vehicle) to analyze the dose-plasma concentration-time relationship of 17P. Participation in the PK substudy will be stratified by pre-pregnancy BMI, into ≤ 28 and > 28 such that approximately 40% and 60% of subjects are expected to be in each BMI category, respectively. In addition, for the third blood sample, subjects will be stratified 2:1 (17P: vehicle) such that an even distribution of samples will be drawn on day 1, day 2, day 3, day 4 or day 5/6 post-dose. This will result in approximately 60 17P and 30 vehicle samples on each day interval.

All subjects randomized into the clinical trial may participate in the PK substudy until the necessary number of subjects in each treatment group and BMI category complete the PK study.

A total of 3 blood samples will be drawn from each subject in the PK substudy:

1. Before study drug dosing at either Visit 6 or 7 (i.e., Dose 5 or 6).
2. Before study drug dosing at either Visit 8 or 9 (i.e., Dose 7 or 8).
3. At a separate, non-dosing visit 1 to 6 days after Visit 9, 10, or 11 (i.e., 1 to 6 days after Doses 8, 9, or 10). Subjects will be stratified 2:1 (17P: vehicle) such that an even distribution of samples will be drawn on day 1, day 2, day 3, day 4 or day 5/6 post-dose.

Samples will be processed and shipped as described in the Study Manual.

8 REPORTING ADVERSE EVENTS

8.1 Definitions

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical event not present prior to exposure to study medication or any event already present that worsens in either intensity or frequency following exposure to study medication from trial injection at Baseline through End of Treatment Period Visit, regardless of its causal relationship to study treatment. Non-treatment-emergent events

(i.e., events occurring prior to study medication exposure) should be recorded as medical history.

A treatment-emergent AE (TEAE) is defined as any event not present prior to exposure to study medication or any event already present that worsens in either intensity or frequency following exposure to study medication from Randomization through End of Treatment Period Visit.

All AEs that occur after trial injection through the End of Treatment Period Visit must be reported in detail on the appropriate eCRF and followed to satisfactory resolution or until the investigator deems the event to be not significant for further follow up. The description of the AE will include the onset date, date of resolution, severity, seriousness (see Section 8.5), and the likelihood of relationship of the AE to study treatment (see Section 8.4). For the purposes of this study, preterm birth and associated neonatal morbidities will not be reported as an AE. Preterm birth and associated neonatal morbidities are an anticipated outcome of this population and will be captured on a specific page in the subject's eCRF but will not be recorded on the AE page.

Because other drugs which contain a castor oil-based vehicle have been associated with rare cases of POME, investigators will be asked to monitor for symptoms of POME, such as transient coughing or dyspnea, for 10 minutes after each injection. Although the volume of castor oil in these other preparations is larger than is used in the study drug, investigators will monitor for the presence or absence of these symptoms and record observations in the eCRF.

A serious adverse event (SAE) is defined as any event that results in maternal, fetal, neonatal death; is immediately life threatening; requires subject inpatient hospitalization (for more than 24 hours) for reasons other than pregnancy complications and/or preterm delivery; or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. For the purposes of this study, hospitalization due to preterm labor/pPROM that does not result in delivery, is expected and will be recorded on the subject's eCRF and not reported as an SAE.

Hospitalization for labor that results in birth is an expected outcome in this population and will be captured in the subject's eCRF (not reported as an SAE). However, complications requiring the mother to remain hospitalized longer than expected will be treated as an SAE.

For the purposes of this study, preterm births that result in admission to the NICU and/or a prolonged stay in the NICU are expected and will be recorded on the subject's eCRF and not reported as an SAE.

For the purposes of this study, all congenital anomalies detected at the time of birth will be recorded in the eCRF and will not be reported as an SAE. Any congenital anomalies that become apparent after birth through 28 days after birth or discharge from the NICU, whichever is later, will be reported as SAEs.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent

one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

8.2 Eliciting Adverse Event Information

Adverse events will be assessed from the time the subject receives the trial injection through 35 ± 7 days after the last dose of study drug.

At every study visit, subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medication, or changed concomitant medication regimens (both prescription and OTC medications).

All randomized subjects, regardless of when they deliver, should be contacted for an End of Treatment Period Visit to obtain AE information including medications to treat AE(s). The contact can be either in person or by telephone and should occur 35 ± 7 days after the last dose of study drug. Maternal or fetal deaths will be recorded through delivery.

If a subject receives the trial injection but is not randomized, adverse events that the investigator becomes aware of should be reported up to 42 days after the trial injection.

8.3 Adverse Event Reporting

All AEs reported or observed during the study will be recorded in the AE eCRF. Information to be collected includes type of event, date of onset, investigator-specified assessment of severity and relationship to study drug, date of resolution of the event, and seriousness. Treatments for AEs will be recorded on the concomitant medications eCRF. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. Medical Dictionary for Regulatory Activities (MedDRA®) version 10.1 or higher will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates or worsens significantly from baseline at any time during the study, it should be recorded as an AE.

8.4 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study medication in causing or contributing to the AE will be characterized using the following classification and criteria:

Definite:

a. A reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues and,
b. Improves or disappears on stopping or reducing the dosage (dechallenge) and,
c. Is an unusual event that is known to be associated with the drug or this class of compound, and cannot be explained by other therapy or the subject's physical condition, or
d. Reappears on a repeated exposure (rechallenge).

Probable:

a. A reaction that follows a reasonable temporal sequence from administration of the drug and,
b. Improves or disappears by dechallenge and,
c. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, and
d. Rechallenge was not attempted.

Possible:

a. A reaction that follows a reasonable temporal sequence from administration of the drug and,
b. It is reasonable to suspect drug causation after considering basic illness, concomitant illness, and other modes of therapy administered to the subject.

Unlikely/Remote:

a. Any reaction not meeting the criteria for definite, probable or possible and,
b. Current knowledge indicates that a relationship is unlikely.

Definitely Not:

a. Any reaction not meeting the criteria for definite, probable or possible and,
b. That is known to be associated with the subject's clinical condition, or with other medication taken by the subject.

8.5 Assessment of Severity

The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild events require minimal or no treatment and do not interfere with the subject’s daily activities.

Moderate events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be recorded to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent (events occurring at irregular or infrequent intervals) require documentation of onset and duration of each episode.

8.6 Serious Adverse Event Reporting

Any AE considered serious by the investigator, or which meets the above criteria must be reported to the sponsor within 24 hours from the time site personnel first learn about the event at the following address:

[redacted]

North America
Hotline: [redacted]
SAE Fax line: [redacted]

Rest of the World
Hotline: [redacted]
SAE fax line: [redacted]

A written report must be submitted within 24 hours of the initial reporting to the sponsor and should consist of the Serious Adverse Event Report Form, accompanied by the following eCRF pages: the demographics page(s), the medical history page(s), the AE page(s) and the concomitant medications page(s). If the subject is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary should be faxed to the sponsor as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the investigator. All SAEs (related or unknown relationship to the study drug) will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the subject to be stable.

The sponsor or its designee will be responsible for reporting SAEs to FDA, EMA and other relevant regulatory authorities according to local regulatory requirements.

The sponsor or its designee will notify FDA, EMA and other relevant regulatory authorities according to local regulatory requirements by telephone or fax transmission of any unexpected, fatal or life-threatening experience associated with the use of the study drug including maternal or neonatal death as soon as possible but no later than 7 calendar days after the initial receipt of the information. If required, initial notification will be followed by a written report within

15 calendar days. For other unexpected events associated with the use of the study drug, the sponsor or its designee will notify FDA, EMA and other relevant regulatory authorities according to local regulatory requirements as soon as possible, but no later than 15 days, of the initial receipt of information. The investigator is responsible for informing the Institutional Review Board (IRB). Copies of SAE correspondence with all investigator, governing authorities, ethics committees, and the sponsor must be submitted to the sponsor for filing.

A subject experiencing 1 or more SAEs will receive treatment and follow-up evaluations by the investigator or will be referred to another appropriate physician for treatment and follow-up.

All AEs, whether serious or nonserious, should be followed to resolution or until the AE is determined by the investigator not to be clinically significant.

8.7 Investigating the Cause of Stillbirth/Fetal Death/In-Utero Fetal Loss

The etiology of a death following a live birth may be different from that of a stillbirth/fetal death/in-utero fetal loss. The investigation of the cause of stillbirth/fetal death/in-utero fetal loss involves evaluation of some fetal and maternal factors and is based on the recommendations from the Stillbirth Collaborative Research Network of the NICHD and the 2009 American College of Obstetricians and Gynecologists (ACOG) guideline on management of stillbirths.[21,22]

The fetal components of the investigation include:

- Autopsy if parental/legal guardian consent is obtained. It should be performed by a pathologist, with perinatal autopsy expertise whenever possible. If consent for autopsy is not obtained, every attempt should be made to gather information through options such as photographs, X-ray imaging, ultrasonography, magnetic resonance imaging or sampling of tissues.
- Placental evaluation along with the cord and the membrane.
- Karyotype if parental/legal guardian consent is obtained to collect tissue/specimen.
- Weight, length and head circumference, and description of any gross abnormalities.

The investigation of the maternal factors that may provide the cause of the stillbirth will involve the performance of the following tests shortly after the delivery:

- Thyroid stimulating hormone,
- Indirect Coombs test (If not performed as part of routine clinical care),
- Serologic test for syphilis,
- Urine toxicology screen,
- Screen for fetal-maternal hemorrhage (Kleihauer-Betke or other) and,
- Parvovirus serology.

Relevant family medical history will also be collected to investigate the etiology of the stillbirth.

If there is clinical suspicion, the following maternal tests will be considered:

- Lupus anticoagulant screen,
- Anticardiolipin antibodies,
- Factor V Leiden mutation,
- Prothrombin G20210A mutation,
- Screen for protein C, protein S, Antithrombin III deficiency and
- Uterine imaging study.

9 STATISTICAL METHODS

9.1 Sample Size

In 3 studies of high-risk pregnant women, the rate of preterm birth < 35^0 weeks of gestation in women receiving vehicle ranged from 26.5% to 30%.[15,23,24] The NICHD study also found that 17.2% of live born infants in women receiving vehicle had the neonatal composite index. Using a 2:1 randomization, a total of 1665 live born infants are required to detect a reduction of 35% in the rate of the composite index (from 17% to 11%) with a power of 90% (assuming a two-sided type I error of 5%). Assuming 2.5% of pregnancies will result in miscarriage or stillbirth, an additional 42 women need to be enrolled for a total of 1707 women (1138 active and 569 vehicle). A total sample size of 1707 subjects provides 98% power to detect a reduction of approximately 30% in the rate of preterm birth < 35^0 weeks of gestation (from 30% to 21%) using a two-sided type I error of 5%. The effect size for the neonatal composite index as well as preterm birth < 35^0 weeks gestation was chosen to represent a clinically significant reduction.

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

There is also sufficient power to detect clinically significant reductions in the secondary outcomes of delivery < 32^0 and < 37^0 weeks of gestation as indicated in Table 3 Sample Size Calculation.

Table 3 Sample Size Calculation

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

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

A fetal/early infant death rate of 4.0% is based on the results of Study 17P-CT-002 (the NICHD 17P trial).

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

9.2 Populations to be Analyzed

Six populations are defined in the analyses:

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

Modified ITT (MITT) Population: MITT Population will consist of all subjects in the ITT Population with outcome data of delivery date available.

Per-Protocol (PP) Population: PP Population will consist of all subjects who are compliant with the study protocol. Each subject will be classified as compliant or not with the protocol based on the following criteria: subject was fully eligible (met all inclusion and had none of the exclusion criteria), at least 90% compliant with study drug, and outcome data available.

Safety Population: The Safety Population will consist of all subjects who received any amount of study drug.

Liveborn Neonate Population: The Liveborn Neonate Population will consist of all babies of randomized women (ITT Population) who were liveborn and have morbidity data available.

Pharmacokinetic (PK) Population: The PK Population will consist of subjects who received study drug and had PK data appropriate for PK analysis. Three blood samples will be drawn from each subject participating in the PK Population portion of the study.

9.3 Statistical Methodology

Inferential statistical analyses as specified will be conducted and all comparisons will be between the 17P and vehicle groups. An alpha level of 0.05 will be used for the co-primary and secondary analyses. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums and maximums for continuous variables will be provided. Listings of individual subjects' data will also be provided. A comprehensive Statistical Analysis Plan will be prepared and finalized prior to database lock and analysis of the data.

9.3.1 Subject Population and Characteristics

Enrollment, protocol deviations, withdrawals from the study (i.e., discontinuation from study drug), and subjects who are lost to follow-up will be summarized by treatment group. Demographics (age, race, marital status, and years of education), pre-pregnancy and enrollment weight/BMI, diabetic status, use of cigarettes, alcohol and street drugs during pregnancy, and obstetrical history (e.g., gestational age of the qualifying delivery, number of previous preterm deliveries, previous miscarriage, previous stillbirth, uterine and vaginal infection or use of corticosteroids prior to randomization, additional risk factors of miscarriage, etc.) will be summarized. Differences between treatment groups will be analyzed using the chi-square or Fisher's exact test for dichotomous variables and the Wilcoxon Rank Sum test for ordinal and continuous variables.

9.4 Efficacy Analysis

9.4.1 Primary Efficacy Outcome Measure

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

H_O: $\prod_{17P} = \prod_V$ and $P_{17P} = P_V$

H_A: $\prod_{17P} \neq \prod_V$ or $P_{17P} \neq P_V$

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

The percentage of subjects with a preterm birth $<35^0$ weeks of gestation will be determined as the point estimate of the survival function from a staggered entry Kaplan-Meier analysis

(which adjusts for gestational age at randomization) using time from randomization to delivery as the analysis variable. Subjects with missing delivery data will be censored at the last known pregnancy. Significant differences between the 17P and vehicle group in the proportion of subjects who deliver prior to 35^0 weeks gestation will be determined using a Cochran-Mantel-Haenszel test stratified by gestational age at randomization (16^0 weeks - 17^6 weeks gestation and 18^0 weeks – 20^6 weeks gestation), where the effective sample sizes for each treatment group and stratum will be derived from Greenwood's formula and a staggered entry Kaplan-Meier analysis using the time from randomization until delivery as the analysis variable. Subjects with missing outcome data will be censored on the date last known pregnant.

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

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

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

9.4.2 Secondary Outcomes

Analysis of the secondary outcome of fetal/early infant death will be conducted in the ITT Population. The relative risk of fetal/early infant death for the 17P group relative to the vehicle group will be determined using the Cochran-Mantel-Haenszel procedure stratified by gestational age at randomization. A two-sided 95% confidence interval (CI) for the relative risk will be constructed using the method of Cochran-Mantel-Haenszel adjusted for gestational age at randomization. If the upper bound of the CI is less than or equal to 2.0, a doubling in the risk of fetal/early infant death can be ruled out. Treatment-by-gestational age at randomization interaction terms will be included in a logistic regression model to determine the relationship, if any, between gestational age at randomization and the risk of fetal/early infant death in the 17P group compared to the vehicle group.

Analyses of the secondary maternal outcomes (delivery $< 32^0$ and $< 37^0$ weeks of gestation) will be conducted using the ITT, Safety and PP Populations. The number and percentages of subjects with delivery $< 32^0$ and $< 37^0$ weeks of gestation will be presented by treatment group and will be determined using the same analytic method as described above for the primary outcome. The number and percentage of subjects with a stillbirth (MITT Population), and whose neonates died (liveborn infants of subjects in the MITT Population) will also be

presented by treatment group. Differences between treatment groups will be analyzed using the Cochran-Mantel-Haenszel test stratified by gestational age at randomization.

9.4.3 Additional Analyses

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

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

9.5 Pharmacokinetic/Pharmacodynamic Analysis

Pharmacokinetic/pharmacodynamic analysis will be conducted in the PK Population. Nonlinear mixed effects modeling will be used to analyze the dose-plasma concentration-time data of 17P using a population PK approach and the NONMEM software [redacted].

As a starting point for the sparse data to be collected in the study, a structural PK model will be initially developed. The structural PK model will contain PK parameters such as clearance and volume as fixed-effect parameters. The dependence of apparent clearances and volumes on BMI will be examined as primary covariate. Based on available literature, it is anticipated that a two-compartment model with first order absorption and elimination rates will be adequate to describe this data.[25-28] In addition, the between-subject (intersubject) variability in the parameter estimates and the random residual error in the data will be estimated with an appropriate error model. The best base model will be selected based on the standard criteria such as minimum objective function value and diagnostic plots.

The relationship of 17P steady-state exposure with the pharmacodynamic (PD) response markers will be defined using an appropriate PK/PD model such as an inhibitory maximum observed effect (E_{max}) model. The selection of a starting base PD model will be based on graphical evaluation of the exposure-response data as well as biological meaningfulness.

The PK Population will be stratified by BMI at the time of randomization. Body mass index will be investigated as the primary covariate for its potential influence on the volume of distribution and clearance of 17P through its formal inclusion in the NONMEM models. Statistical significance will be concluded by suitable reduction in the objective function.

Other factors including race, and number of previous preterm delivery(ies) may be considered as covariates. Findings of a clinical relevant magnitude will be investigated further.

While there exists a number of compounds that interact with progesterone, it is not known what the effect of these compounds will be on 17P. Therefore, PK/PD models to evaluate effects on concomitant medications that may affect the inhibition or induction of HPC will be evaluated and modeled as data permit.

9.6 Safety Analysis

Safety analyses will be conducted in the Safety Population.

Summaries will be provided for all AEs. The incidence of AEs will be presented by system-organ class, higher level term and preferred term according to MedDRA, relationship to study treatment, severity and seriousness. AEs leading to premature discontinuation from the study drug will be summarized in a table.

The percentage of subjects with pregnancy complications including gestational diabetes, oligohydramnios, significant antepartum bleeding or hemorrhage, preeclampsia, gestational hypertension, abruption and chorioamnionitis will be presented and compared between treatment groups using the Cochran-Mantel-Haenszel test stratified by gestational age at randomization.

9.6.1 Interim Analyses

During the trial, an external and independent DSMB will meet periodically to review safety data. The timing of the DSMB reviews and scope of the safety review will be detailed in the DSMB Charter. Since the DSMB will not be reviewing efficacy data, no adjustment to the alpha level is required. The DSMB Charter will indicate whether the data are reviewed in a blinded or unblinded manner.

10 DATA HANDLING AND QUALITY ASSURANCE

10.1 Electronic Case Report Forms

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories.

All eCRF information is to be filled in. If an item is not available or is not applicable, this fact should be indicated. Each completed eCRF must be reviewed, signed, and dated by the investigator in a timely manner.

10.2 Monitoring of the Study

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

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

10.3 Inspection of Records

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

The investigator should promptly notify the sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.4 Study Record Retention

Essential documents will be retained until at least 2 years have elapsed since the formal discontinuation of the clinical trial of 17P. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

11 ADMINISTRATIVE CONSIDERATIONS

The following administrative items are meant to guide the investigator in the conduct of the trial but may be subject to change based on industry and government Standard Operating Procedures or Working Practice Documents or Guidelines. Changes will be reported to the IRB/IEC, but will not result in protocol amendments.

11.1 Confidentiality

All PK specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, applicable regulatory authorities, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2 Institutional Review Board /Independent Ethics Committee Approval

National regulations and the ICH guidelines require that approval be obtained from an IRB/IEC prior to participation of human subjects in research studies. Prior to the study onset, the protocol, informed consent, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to the subject or the subject's legal guardian and must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH Guideline E6 will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC Chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title and/or protocol number and the date approval and/or favorable opinion was granted.

The investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must supply the sponsor or its designee with written documentation of continued review of the clinical research.

11.3 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval prior to subjects being enrolled into an amended protocol.

11.4 Informed Consent

A written informed consent in compliance with ICH and Part 50 of Title 21 of the Code of Federal Regulations (CFR) shall be obtained from each subject/legal guardian prior to entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. If permitted by local regulations and approved by the applicable ethics committee/IRB, subjects may use a computerized learning tool as part of the informed consent process. If required by local regulations, consent must be obtained from parent(s)/legal guardians to collect data on neonates. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor and/or its designee, if appropriate prior to IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval prior to the start of the study. If a protocol amendment significantly alters the study design, increases potential risk to the subject, or otherwise affects statements in the ICF, the ICF must be revised accordingly and submitted to regulatory authorities and/or IRB/IECs as required for review and approval. The approved ICF must be used to obtain informed consent from new subjects prior to randomization and must be used to re-obtain informed consent from subjects currently participating in the study if they are affected by the amendment as determined by local regulatory requirements. For purposes of this study, a subject is considered currently

participating if they have not yet completed protocol-related procedures associated with whichever of the following protocol events occurs latest:

- End of Treatment Period Visit date (to occur 35 ± 7 days after receipt of last dose of study drug)
- 28 days following neonate delivery
- Discharge of the neonate from the NICU (only applicable if the neonate was admitted into the NICU)

At centers participating in the 17P-FU-004 study, every effort will be made to obtain informed consent for the 17P-FU-004 study from all randomized subjects while they are pregnant. If it is not possible to obtain consent during the pregnancy, consent may be obtained up to the point that their child reaches one year of age. Agreement to participate in the follow-up study is not required to participate in this study. Every attempt will be made to keep study subjects and clinical site staff blinded to treatment assignment.

Women who need translation assistance will be enrolled by a person fluent in their language and both verbal and written informed consent obtained in that language; if such are not available, they will not be included.

Before recruitment and enrollment, each prospective subject and/or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The investigator shall provide a copy of the signed ICF to the subject and/or legal guardian. The original form shall be maintained in the subject's medical records at the site.

11.5 Protocol Deviations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. Protocol deviations will also be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified of deviations in writing by the monitor. The IRB/IEC should be notified of significant protocol deviations in a timely manner.

11.6 Study Reporting Requirements

By participating in this study the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to his/her IRB/IEC as appropriate. The investigator also agrees to provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study.

11.7 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

The sponsor is not financially responsible for further testing/treatment of any medical condition that may be detected during the baseline process. In addition, in the absence of specific arrangements, the sponsor is not financially responsible for further treatment of the subject's disease.

11.8 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH Guidance E6 8.2 and Title 21of the CFR by providing the following essential documents, including but not limited to:

- An original investigator-signed Investigator's Agreement page of the protocol.
- An IRB/IEC-approved ICF, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject/legal guardian.
- IRB/IEC approval.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
- Curriculum vitae (CV) for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the CV. They will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

11.9 Study Conduct

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

11.10 Publications

Following completion of the study, the data will be considered for reporting at a scientific meeting or for publication in a scientific journal. A publications committee comprised of representatives of the sponsor and leading investigators will be established to oversee all publications from the study. The publications committee will recommend how the primary multi-site manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The publications committee will make similar recommendations for any proposed publication involving subjects from multiple institutions.

Publication of the results of the Study results at any individual site shall not be made before the first multi-site publication.

12 INVESTIGATOR'S STATEMENT

By signing below, I acknowledge the Clinical Research Study presented in this protocol is clearly understood and agreed upon. The effort is feasible in terms of resources and testing requirements. I agree to conduct the study as outlined in the protocol entitled, "A Phase 3B, Multi-center, Randomized, Double-blind Study of Hydroxyprogesterone Caproate Injection, 250 mg/mL, Versus Vehicle for the Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery" in accordance with the guidelines and all applicable government regulations including Part 54 of Title 21 of the CFR. I have read and understand all sections of the protocol, including Section 11, Administrative Considerations.

<Principal Investigator's Name>	Date

13 MATERNAL COMPLICATIONS AND NEONATAL OUTCOMES

13.1 Maternal Pregnancy Complications

- **Gestational Diabetes**: Any degree of glucose intolerance with onset or first recognition during the current pregnancy. A fasting plasma glucose level >126 mg/dL (7.0 mmol/L) or random plasma glucose >200 mg/dL (11.1 mmol/L) meets the threshold for the diagnosis of diabetes, if confirmed on a subsequent day, and precludes the need for any glucose challenge. [29]
- **Oligohydramnios**: Using ultrasound, amniotic fluid index (the sum of measurements of the deepest cord-free amniotic fluid pocket in each of the abdominal quadrants) less than 5 cm or if clinically diagnosed.
- **Significant antepartum bleeding or hemorrhage**: Bleeding after the subject was randomized, including placenta previa, abruption placenta, or threatened abortion. Spotting is not considered significant.
- **Gestational Hypertension:** Having 2 blood pressures ≥140/90 mmHg on at least 2 occasions (4 or more hours apart) and a clinical diagnosis of gestational hypertension (without proteinuria or other signs of preeclampsia).
- **Preeclampsia:** Within a 24-hour period having blood pressure measurements ≥140/90 mmHg on at least 2 occasions (4 or more hours apart) and proteinuria of 0.3 g or greater in a 24-hour urine specimen or +1 or greater protein on urine dipstick.
- **Eclampsia:** Occurrence of generalized convulsion and/or coma in the setting of preeclampsia, with no other neurological condition.
- **HELLP Syndrome:** Meets all three of the following conditions
    1. Hemolysis: abnormal peripheral smear, increased bilirubin >1.2 mg/dL
    2. Elevated liver enzymes: aspirate aminotransferase (AST) ≥72 IU/L, lactate dehydrogenase (LDH) >600 IU/L; and
    3. Thrombocytopenia: platelet count <100,000/mm^3
- **Abruption**: Diagnosed clinically with placental abruption (retroplacental hematoma). Do not include abruption diagnosed by pathologist's report.
- **Chorioamnionitis**: Clinical diagnosis of chorioamnionitis and body temperature of ≥ 100ºF (37.8ºC) and no other defined infection. Maternal physical symptoms may include the following: fever: body temperature of ≥ 100ºF (37.8ºC) and no other defined infection, tachycardia (>120 beats per minute), hypotension, diaphoresis, cool or clammy skin, uterine tenderness, and foul-smelling or abnormal vaginal discharge. The fetus may present with tachycardia (>160 beats per minute).

  Does not include chorioamnionitis diagnosed only by a placental pathology report.

- **Placenta Previa**: Implantation of the placenta over or near the internal os of the cervix.

13.2 Neonatal Outcomes

- **Neonatal Death**: Death of a liveborn infant from minutes after birth until 28 days of life. Note: for the purposes of the neonatal morbidity and mortality index only, a death prior to discharge from the NICU will also be counted as a neonatal death.
- **Transient Tachypnea (TTN)**: Term or late preterm infant presents in the first hours after birth with mild cyanosis and respiratory distress (grunting, nasal flare, chest retractions and/or tachypnea). The chest films shows perihilar streaky infiltrate. Final clinical impression excludes pneumonia or RDS Type I.
- **Respiratory Distress Syndrome (RDS):**

  Must meet both criteria A and B below:
  A. PaO_2 <50 mmHg in room air, central cyanosis in room air, a requirement for supplemental oxygen to maintain PaO2 >50 mmHg, or a requirement for supplemental oxygen to maintain a pulse oximeter saturation over 85% **within the first 24 hours of life.**
  AND
  B. A chest radiograph consistent with RDS (for example, reticulogranular appearance to lung fields with or without low lung volumes and air bronchograms) **within the first 24 hours of life.**
  Note: Include diagnosis of hyaline membrane disease, Type I RDS, hyaline membrane disease and respiratory insufficiency of prematurity. Do not include transient tachypnea of the newborn (TTN or Type II RDS). Do not include (brief) 'blow by' oxygen administration.
- **Bronchopulmonary Dysplasia (BPD):** Chronic lung disease, defined as
  - Respiratory symptoms ***and***
  - Chest radiograph abnormalities ***and***
  - A requirement for supplemental oxygen in an infant born <32 weeks who is now 36 weeks post menstrual age (PMA).
- **Persistent Pulmonary Hypertension of the Newborn (PPHN):** Diagnosed clinically by echocardiogram or catheterization.
- **Duration of Ventilator Support:** The total calendar days, including multiple periods on the ventilator. This refers to mechanical ventilation only that is the infant was on a ventilator with a rate recorded and does not include CPAP. This does include the use of synchronized mechanical ventilation **(SIMV)** but does not include simultaneous combination of CPAP with mechanical ventilation, sometimes referred to as cycled CPAP. Count the number of calendar days on which the infant received treatment at some point during the day (e.g., if the infant was started at noon on one day and taken off at noon the following day, this would count as two calendar days rather than one day).
- **Duration of Oxygen Therapy:** The number of calendar days that the infant received supplemental oxygen ($Fi0_2 > 0.21$) after admission to nursery from Labor and Delivery (e.g., if the infant was started at noon on one day and taken off at noon the following

day, this would count as two calendar days rather than one). Do not include "blow by" oxygen administration. Record "000 if no oxygen was administered outside Labor and Delivery. If infant receives oxygen while also on the ventilator include those hours in the totals for both duration of ventilator support and duration of oxygen therapy.

- **Patent Ductus Arteriosus (PDA):** Clinical evidence of left to right PDA shunt documented by continuous murmur, hyperdynamic precordium, bounding pulses, wide pulse pressure, congestive heart failure, increased pulmonary vasculature or cardiomegaly by CXR, and/or increased oxygen requirement or ECHO evidence of PDA with documentation of left to right ductal shunting.
- **Seizures:** 3 level categorical variable: No, Suspect, Yes.

  Suspect – when attending physician records questionable seizures
  Yes – when the attending physician believes that seizures definitely occurred. A positive EEG may be available to confirm the diagnosis.

- **Intraventricular Hemorrhage (IVH):** Bleeding from blood vessels in the periventricular germinal matrix of the brain. The hemorrhage may be confined to the matrix or may extend to the ventricles and the parenchyma of the brain.

  The degree of IVH is graded as None, Grade I, Grade II, Grade III and Grade IV (5 level categorical variable).

  Grade I – Isolated subependymal hemorrhage
  Grade II – IVH without ventricular dilation
  Grade III – IVH with ventricular dilation
  Grade IV – IVH with parenchymal extension

  Note: The grade of the hemorrhage will be determined by the most severe cranial imaging finding prior to discharge and will be recorded according to the system of Papile et al.[30] Do not use the grade indicated on the autopsy report. Diagnosis should be made either by Ultrasound, CT or MRI.
- **Periventricular Leukomalacia (PVL):** Defined by the following[31]:
  - Grade I involves periventricular flares persisting for more than 7 days
  - Grade II indicates small periventricular cysts
  - Grade III is defined as extensive periventricular cysts
  - Grade IV is multicystic leukomalacia in the periventricular and subcortical region
- **Retinopathy of Prematurity (ROP) Stage:** Defined by the worst stage documented on any exam in the eye with the most advanced stage.
- **Proven Sepsis:** If an infant has at least one of the following signs/symptoms or in the judgment of the investigator has other symptoms that are indicative of sepsis, the physician should order appropriate cultures to document sepsis.

Sign/Symptom	Blood Culture	Urine Culture	CSF Culture
Fever (>38ºC core)	X	X	X
Hypothermia (<37ºC core)	X	X	X
Apnea	X	X	X
Bradycardia	X	X	X
Dysuria		X	
Lethargy		X	
Vomiting		X	
Stiff neck			X
Meningeal signs			X
Cranial nerve signs			X
Irritability			X

The infant must have a positive blood, urine or CSF culture to be recorded as proven sepsis.

In the case of a positive blood culture the infant must either have two cultures within a 3 calendar day period showing the same organism or the investigator must document that, in his/her judgment:

- Other causes of infection have been ruled out
- A single positive blood culture is not due to a skin contaminant

In the case of a positive urine culture, the culture must also meet the following criterion:

- The culture has $\geq 10^5$ microorganisms per cc of urine and no more than two species of microorganisms.

If the infant does not have a positive blood, CSF or urine culture for the purposes of study documentation a diagnosis of proven sepsis cannot be made, even if the investigator makes a clinical diagnosis of sepsis and treats the subject with antibiotics.

- **Confirmed Pneumonia:** Pneumonia diagnosed clinically within 72 hours of birth and confirmed by either an x-ray demonstrating consolidation with air bronchograms, or a positive blood culture performed at the time of clinical diagnosis.
- **Necrotizing Enterocolitis (NEC):** Presence of one or more of the following clinical signs: bilious gastric aspirate or emesis, abdominal distension, occult or gross blood in stool (no fissure) AND one or more of the following radiographic findings present: pneumatosis intestinalis (cystic or linear), hepato-biliary gas, pneumoperitoneum.
- **Neonatal Hypoglycemia:** Newborns with a plasma glucose concentration less than 40 mg/dL (2.2 mmol/L) during the first 24 hours of life and less than 50 mg/dL (2.8 mmol/L) after 24 hours of age.[32]

14 LIST OF DRUGS METABOLIZED BY CYP1A2, CYP2A6, AND CYP2B6

Possible P450 Drug Interactions[33-35]

CYP1A2	CYP2A6	CYP2B6
Amitriptyline	Acetaminophen	Bupropion
Caffeine	Coumarin	Cyclophosphamide
Clomipramine	Fadrozole	Efavirenz
Clozapine	Halothane	Ifosphamide
Cyclobenzaprine	Nicotine	Methadone
Estradiol	Valproic acid	Sorafenib
Fluvoxamine		
Haloperidol		
Mexiletine		
Naproxen		
Olanzapine		
Ondansetron		
Phenacetin		
Acetaminophen		
Propranolol		
Riluzole		
Ropivacaine		
Tacrine		
Theophylline		
Tizanidine		
Verapamil		
(R)-Warfarin		
Zileuton		
Zolmitriptan		

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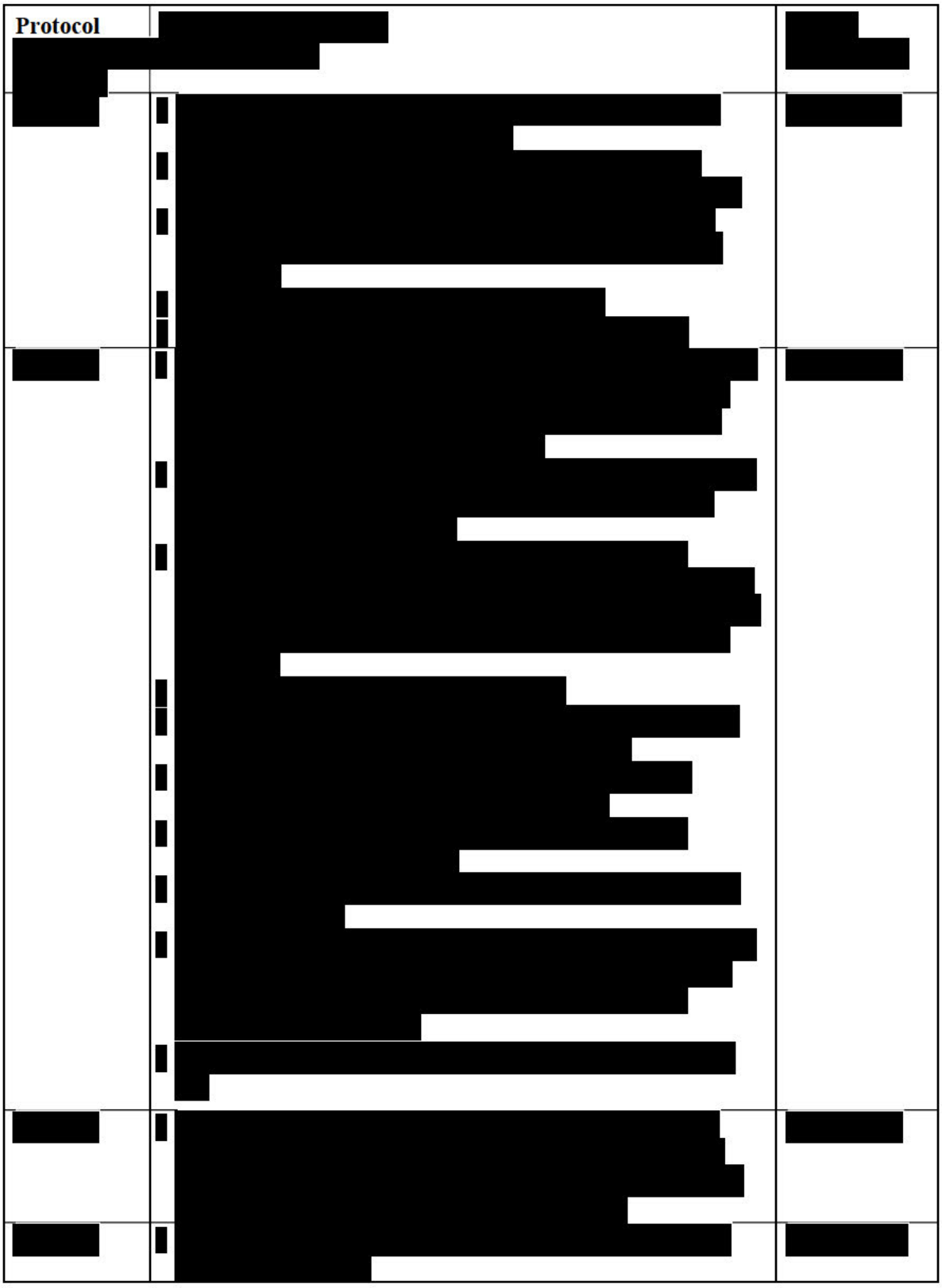
Summary of Changes



Summary of Changes

Protocol Amendment (Version)	Subject of Amendment (Main Changes)	Date of Amendment
[redacted]	[redacted]	[redacted]