GTITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	Randomized, Double-Blind, Multicenter, Phase III Study Comparing the Efficacy and Safety of Retosiban Versus Placebo for Women in Spontaneous Preterm Labor

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N194467_00	2014-NOV-26	Original
2014N194467_01	2015-FEB-17	Republished
The protocol was republished to make Section 6.4 (Blinding) consistent with the protocol template.		
2014N194467_02	2015-AUG-13	Amendment No. 1
The following changes are reflected in Protocol Amendment No. 1: • Revise the time-to-delivery co-primary endpoint into a composite endpoint consisting of (1) time to delivery or (2) time to treatment failure, whichever occurs first • Revise the description of the study design to indicate that investigators have discretion to use a standardized regimen of magnesium sulfate • Revise the description of the study design to indicate that investigators have discretion to use intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection • Revise to standardize the magnesium sulfate regimen in order to avoid wide variations in the magnesium sulfate dose given to subjects • Revise to standardize the betamethasone or dexamethasone regimen in order to control for wide variations in the antenatal corticosteroid doses • Add the secondary endpoints of (1) time to delivery, (2) time to treatment failure, and (3) proportion of women receiving any putative tocolytic • Revise the guidance regarding an adequate treatment response to be based on (1) a clinically relevant reduction of contraction frequency and/or intensity or (2) no change in the cervical examination • Provide the volume of maternal blood that will be collected for hematology, chemistry, and liver function tests; biomarker analyses; genetic analyses; and pharmacokinetic analyses • Add guidance for monitoring the total volume of oral and intravenous fluid administered during preterm labor • Remove the requirement to collect a placental tissue sample for pathologic examination • Remove the requirement to collect cord blood samples for biomarker and genetic testing • Add that US and Canadian investigational centers will collect a maternal blood		

sample for cell-free fetal DNA in women who provide informed consent for genetic research

- Clarify that any SAEs and AEs of special interest that are unresolved at 28 days post EDD should be followed to stabilization or resolution in those infants participating in the follow-up study.
- Add the prohibition of calcium-channel blockers, nonsteroidal anti-inflammatory drugs, and β-agonists either for tocolysis during investigational product administration or for maintenance tocolysis in subjects who remained undelivered following the Inpatient Treatment Phase
- Revise the statistical methodology to control the Type I error for the planned interim analyses
- Incorporate other administrative changes

2014N194467_03	2015-SEP-14	Amendment No. 2

The following changes are reflected in Protocol Amendment No. 2:

- Revise the guidance for administration of antenatal corticosteroids to read as follows: If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours. A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least 7 days prior to study enrollment.
- Clarify in the Time and Events Table (footnote 15) that hematology, chemistry, and liver function tests will only be determined through a central laboratory at the screening, Day 2, and the face-to-face post-infusion assessment visits.
- Incorporate other administrative changes

2014N194467_04	2016-APR-19	Country-Specific Protocol Amendment for Sites in Italy(Amendment No. 3)

The following changes are reflected in the Country-Specific Protocol Amendment for Italy:

- Amend inclusion criteria 1 and 2 to specify that subjects must be at least 18 years of age to participate in Study 200719. Text was revised throughout to reflect the change in the subject age criterion.
- Revise text throughout to indicate that subjects recruited into Study 200719 in Italy must not be dosed with the investigational product until the results of their chemical parameters have been reviewed by the Investigator and no indicators of altered liver function (AST and ALT values and bilirubinemia) are apparent. This check for altered liver function must be carried out before the study drug is administered, i.e., before initiating randomized treatment.

2014N194467_05	2016-JUN-20	Amendment No.4

The following changes are reflected in Protocol Amendment No. 4:

- Add the proportion of women experiencing subsequent episodes of preterm labor as a supportive other secondary endpoint.
- Clarify the assessments performed at the 1-week face-to-face post-infusion visit and at the weekly telephone calls during the Post-Infusion Assessment Phase.
- Clarify the concomitant medications that are considered putative tocolytics and add exceptions for putative tocolytic drug use with regard to the definition of treatment failure.
- Clarify the methods for documentation of gestational age at Screening.
- Add that manual palpations may be used for determining contraction frequency in situations where technical difficulties may prohibit accurate measurement.
- Clarify the criteria for confirming sufficient dilation and effacement at Screening.
- Clarify that withdrawal from the study will mean that no additional visits can occur or procedures performed.
- Define inadequate treatment response.
- Add procedures that should be followed for managing dose interruptions.
- Add that subject use of a pessary is allowed if use began before the current episode of preterm labor; otherwise, use of a pessary is prohibited.
- Revise the previous requirements for continuous fetal heart rate monitoring to electronic fetal monitoring for a minimum of 6 hours from the start of the infusion or from the start of a dose increase, provided the heart rate pattern is consistently reassuring.
- Clarify that confirmation of uterine contraction eligibility criterion must occur within 60 minutes before study drug dosing.
- Add respiratory rate to the vital sign measures assessed during the study, and clarify the frequency that vital sign and oxygen saturation measurements are assessed relative to dosing.
- Clarify that if a subject does not deliver at the investigative center, central laboratory assessments for hematology, chemistry, and liver function tests should be performed at the investigative center within 1 week (acceptable range: 3 to 14 days) after completion of the study drug infusion.
- Revise the visit window for the administration of the Edinburgh Postnatal Depression Scale from ±2 weeks to ±6 weeks.
- Clarify that a maternal blood sample for PK analyses may need to be collected at the same time as the cord blood sample if the sample time does not already coincide with a PK sampling window.
- Revise the assessment requirement for the first interim analysis from the time when

approximately 150 women/pairs complete all assessment to the time when approximately 150 subjects have time-to-delivery results available.

- Clarify that the second interim analysis will occur when approximately 400 women/newborn pairs are followed up to 28 days post EDD.
- Add an appendix that provides guidelines for reporting maternal, fetal, and neonatal adverse events (AEs) of special interest.
- Clarify that the intensity categories for AEs and serious AEs can be found in the Study Procedures Manual.
- Incorporate the changes detailed in the country-specific amendment for sites in Italy (dated 19 Apr 2016).
- Incorporate other administrative changes.

2014N194467_06	2017-JAN-05	Amendment No. 5

The following changes are reflected in Protocol Amendment No. 5:

- Remove screening urine drug and alcohol tests.
- Remove requirement that investigator confirm uterine contraction rate and cervical dilation after randomization and just before study drug administration.
- Add that after randomization and prior to study drug administration investigators will re-assess that tocolytic therapy is still indicated, according to their medical discretion.
- Clarify that an abdominal ultrasound to assess fetal growth is needed at Screening unless the most recent ultrasound is within 3 weeks (21 days) before the date of randomization.
- Update the list of maternal disease-related events to clarify the reporting process for events of subsequent preterm labor and hospitalization for delivery that are not worse than expected.
- Add that the amniotic fluid index should be measured using the 4-quadrant method.
- Incorporate other administrative changes.

SPONSOR SIGNATORY

Kathleen J Beach, MD, MPH Medicine Development Leader, Maternal and Neonatal Health Unit Alternative Discovery and Development	Date

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number	After-Hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD MD	PPD PPD	PPD PPD	PPD PPD	PPD Pharmacovigilance
Secondary Medical Monitor	PPD MD	PPD PPD	PPD PPD	PPD PPD	PPD Pharmacovigilance
SAE Fax Number				PPD PPD	

Sponsor Legal Registered Address:

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s):

IND Number: 73287
EudraCT Number: 2014-003326-41

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 200719 (NEWBORN-1)

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 200719

Rationale

Retosiban (GSK221149), a nonpeptide small molecule that behaves as a selective, competitive antagonist for oxytocin receptors, has been shown to prolong pregnancy and reduce prematurity rates in women between $30^{0/7}$ and $35^{6/7}$ weeks' gestation. Given intravenously over 48 hours, retosiban increased days to delivery by a mean of 8.2 days relative to placebo and the incidence of birth prior to 37 weeks' gestation was 18.7% in retosiban group compared with 47.2% in the placebo group. No placebo-controlled tocolytic studies have demonstrated an effect of this magnitude in spontaneous preterm labor. External experts have generally agreed that prolonging the time to delivery by 1 week in the absence of harm may benefit the newborn, particularly in women who experience spontaneous preterm labor at early gestational ages (GAs).

This study (NEWBORN-1) aims to show that retosiban provides additional neonatal benefit through its effect to arrest labor and prolong pregnancy sufficiently to allow for fetal maturation without significant increased risk to the fetus or neonate. Clinical validation of the relationship between prolongation of pregnancy and neonatal benefit would establish retosiban as the first drug to add benefit to that of the well-established benefits of antenatal corticosteroids for this indication.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• To demonstrate the superiority of retosiban to prolong pregnancy and improve neonatal outcomes compared with placebo	• Time to delivery or treatment failure, whichever occurs first • Proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite determined up to 28 days after the estimated date of delivery (EDD) of $40^{0/7}$ weeks
Secondary	
• To describe the maternal, fetal, and neonatal safety profile during and after intravenous (IV) retosiban treatment compared with placebo	**Maternal:** • Incidence of reported adverse events (AEs) and serious AEs (SAEs) • Significant changes in vital signs and clinical laboratory tests • Incidence of clinical and laboratory toxicities causing subject to discontinue study treatment • Incidence of women scoring 12 or higher on the Edinburgh Postnatal Depression Scale • Maternal AEs of special interest

Objectives	Endpoints
	Fetal: • Incidence of reported AEs and SAEs • Fetal acidosis • Fetal AEs of special interest **Neonatal:** • Neonatal Apgar scores • Growth parameters • Incidence of reported AEs and SAEs • Neonatal AEs of special interest
• To determine the effect of retosiban treatment compared with placebo on health care resource use for the maternal and neonatal hospitalizations	• Assess maternal and neonatal health care resource use associated with preterm labor and preterm delivery
• To obtain further data on the pharmacokinetics of retosiban in pregnant women, including the effect of covariates such as age, weight, race/ethnicity, and GA on retosiban clearance and volume of distribution	• Retosiban clearance and volume of distribution and the effect of covariates on these parameters

Overall Design

- NEWBORN-1 is a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study
- Eligible subjects will be randomly assigned in a 1:1 ratio to receive either retosiban IV infusion over 48 hours or matched placebo IV infusion over 48 hours
- If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours. A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least 7 days prior to study enrollment. Investigators have discretion to use a standardized regimen of magnesium sulfate, as well as intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection.
- Prior to randomization, each subject will be stratified by progesterone treatment at Screening (subjects on established progesterone therapy vs subjects not on established progesterone therapy) and GA ($24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$, or $31^{0/7}$ to $33^{6/7}$)

Treatment Arms and Duration

- NEWBORN-1 will comprise 6 phases: Screening, Inpatient Randomized Treatment, Post-Infusion Assessment, Delivery, Maternal Post-Delivery Assessment, and Neonatal Medical Review. The duration of any subject's (maternal or neonatal) participation in the study will be variable and dependent on GA at study entry and the date of delivery
- Retosiban treatment will be administered as a 6-mg IV loading dose over 5 minutes followed by a 6-mg/hour continuous infusion for the remainder of the 48-hour treatment period.
- The placebo control will be a normal saline (0.9% sodium chloride) infusion matched for the retosiban volume, IV loading dose over 5 minutes, and continuous infusion rate for the remainder of the 48-hour treatment period
- An adequate response is based on (1) a clinically relevant reduction of contraction frequency and/or intensity or (2) no change in the cervical examination.
- Subjects with an inadequate response any time after the first hour of treatment will be administered another 6-mg retosiban or matched placebo loading dose and the retosiban or matched placebo infusion rate will be increased to 12 mg/hour for the remainder of the 48 hour treatment period.
- At each of the 2 planned interim analysis, all available safety and efficacy data will be reviewed by the unblinded independent data monitoring committee who may make recommendations to terminate the study based on prespecified criteria or at any time for an unfavorable benefit:risk profile

Type and Number of Subjects

The study population is women aged 12 to 45 years with an uncomplicated singleton pregnancy in preterm labor with intact membranes between $24^{0/7}$ and $33^{6/7}$ weeks' gestation. Approximately 900 women (450 per treatment group) will be randomly assigned to ensure that approximately 800 women/newborns have recorded birth data (assumes approximately 10% missing data).

Italian Subjects: In Italy, the age restriction for study enrollment is 18 to 45 years.

Analysis

The primary comparison of interest is retosiban versus placebo for the co-primary endpoints: time to delivery or treatment failure, whichever occurs first, and neonatal composite outcome. The statistical analysis will test the null hypothesis in the Intent-to-Treat Population that there is no difference between retosiban and placebo versus the alternative hypothesis that there is a difference between the 2 co-primary endpoints.

Two interim analyses are planned. The first interim analysis will occur after approximately 150 subjects have completed delivery and have time-to-delivery results available. The second interim analysis will occur after approximately 400 women/newborn pairs are followed up to 28 days post EDD.

2. INTRODUCTION

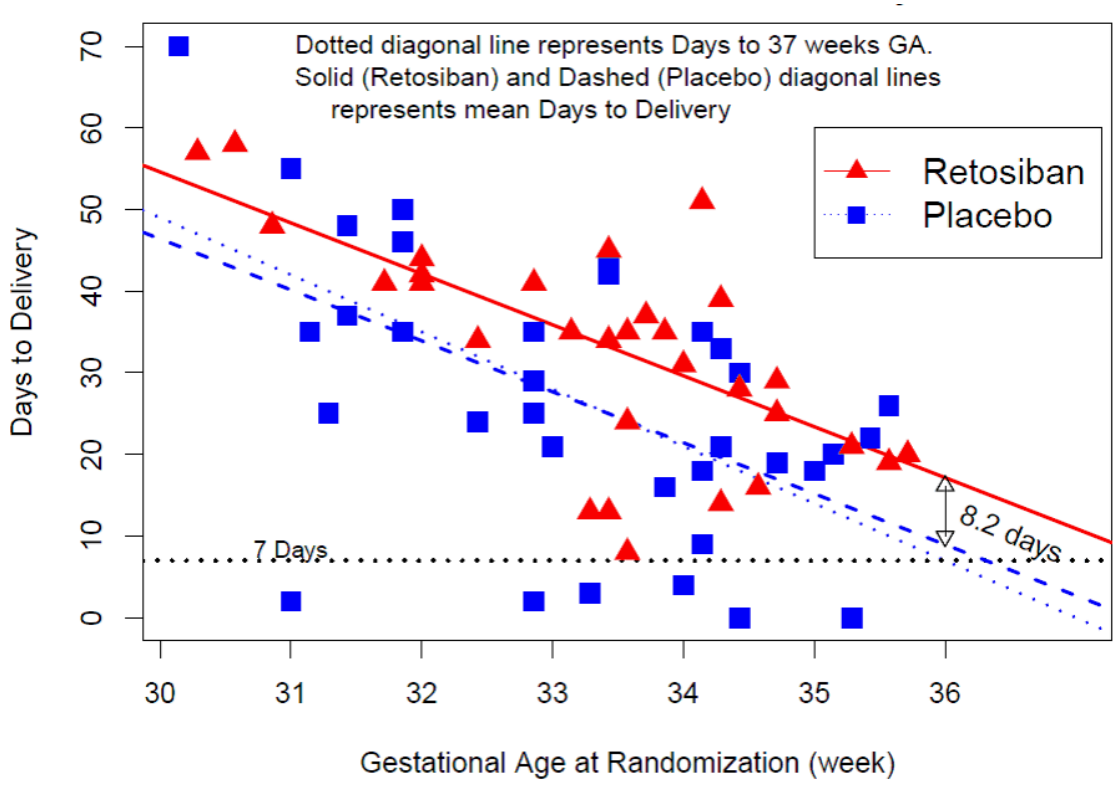
Retosiban (GSK221149) is nonpeptide small molecule that behaves as a selective, competitive antagonist for oxytocin receptors. Retosiban is being developed as a solution for intravenous (IV) infusion for the treatment of spontaneous preterm labor in women with an uncomplicated pregnancy and intact membranes.

2.1. Study Rationale

The inverse relationship between neonatal mortality and morbidity and gestational age (GA) at birth has been the basis for treatments to prolong pregnancy with the goal of improving neonatal outcomes by allowing continued maturation of fetal organ systems. Inhibition of uterine contractions as a means to reduce prematurity rates has been extensively investigated. However, there is no evidence that current tocolytic regimens improve neonatal or infant outcomes beyond the effect of antenatal corticosteroids [Sanchez-Ramos, 1999; Royal College of Obstetricians and Gynecologists; RCOG Green-top Guideline No. 1B, 2011a; American College of Obstetricians and Gynecologists; ACOG Practice Bulletin No. 127, 2012; Roos, 2013]. As a result, tocolytic therapy is only recommended for short-term delay of delivery in order to administer antenatal corticosteroids and in utero transfer to a neonatal specialized care unit.

In contrast, results from the OTA10256 Phase II placebo-controlled study found that retosiban prolonged pregnancy and reduced prematurity rates in women between $30^{0/7}$ and $35^{6/7}$ weeks' gestation. Retosiban, given intravenously over 48 hours, increased days to delivery by a mean of 8.2 days relative to placebo; this difference was consistent across GAs (Figure 1). The incidence of birth prior to 37 weeks' gestation in the retosiban group was 18.7% compared with 47.2% in the placebo group (see the investigator's brochure [IB] Section 5.3.2.2.2 [GlaxoSmithKline Document Number CM2006/00201/05]). No placebo-controlled tocolytic studies have demonstrated an effect of this magnitude in spontaneous preterm labor. External experts have generally agreed that prolonging the time to delivery by 1 week in the absence of harm may benefit the newborn, particularly in women who experience spontaneous preterm labor at early GAs.

Figure 1 Retosiban Effect on Time to Delivery



The emerging safety profile for retosiban also appears favorable. All reported adverse events (AEs) (maternal, fetal, and neonatal) were generally similar to placebo or consistent with expected events in the population under study. A summary of the complete results for Study OTA105256 is included in the IB (Section 5.3.2.1 [GlaxoSmithKline Document Number CM2006/00201/05]).

This study (NEWBORN-1) aims to show that retosiban provides additional neonatal benefit through its effect to arrest labor and prolong pregnancy sufficiently to allow for fetal maturation without significant increased risk to the fetus or neonate. Clinical validation of the relationship between prolongation of pregnancy and neonatal benefit would establish retosiban as the first drug to add benefit to that of the well-established benefits of antenatal corticosteroids for this indication.

2.2. Brief Background

Spontaneous preterm labor is responsible for more than half of preterm births, with the remainder resulting from preterm premature rupture of membranes (PPROM) and clinical indications for delivery in at-risk mothers and fetuses [Goldenberg, 1998; Meis, 1998; Pennell, 2007]. The pathogenesis of spontaneous preterm labor is not well understood. Clinical and experimental studies provide evidence that 4 separate pathways can result in premature labor and delivery: inflammation, maternal-fetal endocrine activation, abnormal uterine distension, and decidual hemorrhage [Romero, 1994; Lockwood, 2001].

The use of tocolytics to prevent preterm birth has been based on the assumption that clinically apparent contractions signal the initiation of parturition [Simhan, 2007]. Stopping contractions would therefore halt labor progression, prolong the pregnancy, and reduce neonatal morbidity and mortality. However, when examining the benefits of tocolysis, systematic reviews have consistently concluded that current tocolytic treatment does not provide direct benefit in terms of neonatal mortality, neonatal morbidity, or perinatal outcome beyond that of antenatal corticosteroids [Gyetvai, 1999; Sanchez-Ramos, 1999; RCOG Green-top Guideline No. 1B, 2011a; ACOG Practice Bulletin No. 127, 2012].

Despite the lack of direct neonatal benefit, controlled studies have generally shown that tocolysis reduces the likelihood of delivery within 48 hours or 7 days following initiation of treatment. Based on these findings, practice guidelines advise physicians to consider tocolysis in those women for whom a delay in delivery would benefit the newborn via administration of antenatal corticosteroids or in utero transfer to a specialized care unit [RCOG Green-top Guideline No. 7, 2010; ACOG Practice Bulletin No. 127, 2012].

Oxytocin is a potent uterotonic whose role in the initiation and progression of human labor, both term and preterm, has been actively investigated for many years. Although preterm labor may well be a syndrome with various etiologies, oxytocin action on the uterus likely represents a common step in activation of the myometrium. Paracrine rather than endocrine mechanisms may mediate this process, in which the effects of oxytocin are governed by tissue-specific oxytocin receptor expression, which leads to direct contractile effects in myometrium and prostaglandin formation in the decidua. Prostaglandins in turn mediate myometrial contractions and cervical ripening [Fuchs, 1982; Benedetto, 1990].

Retosiban (GSK221149) is a nonpeptide small molecule that behaves as a selective, competitive antagonist for oxytocin receptors and is under development for the treatment of spontaneous preterm labor in women with intact membranes. NEWBORN-1 is designed to show that retosiban provides neonatal benefit beyond that of antenatal corticosteroids through its effect to arrest labor and prolong pregnancy sufficiently to allow for fetal maturation without increased risk to the fetus or neonate.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	

• To demonstrate the superiority of retosiban to prolong pregnancy and improve neonatal outcomes compared with placebo	• Time to delivery or treatment failure, whichever occurs first. Time to delivery will be calculated from the start of study treatment administration until delivery. Time to treatment failure will be calculated from the start of study treatment administration to the administration of any putative tocolytic medication
	• Proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite determined up to 28 days after the estimated date of delivery (EDD) of $40^{0/7}$ weeks:
	  • Fetal or neonatal death
	  • Respiratory distress syndrome (RDS)
	  ○ Requiring continuous positive airway pressure or mechanical ventilation. Diagnosis requires a chest radiograph consistent with RDS (reticulogranular appearance to the lung fields or air bronchograms) within the first 24 hours of life, OR
	  ○ Received surfactant for a clinical picture of RDS within the first 24 hours of life
	  • Bronchopulmonary dysplasia at ≥36 weeks postmenstrual age (determined by adding chronological age to GA at delivery), defined as follows:
	  ○ >21% supplemental oxygen requirement, OR
	  ○ Use of high-flow nasal cannula at ≥1 L (21% oxygen)
	  • Necrotizing enterocolitis or isolated perforation
	  ○ Diagnosed by radiographic evidence of Stage II or higher according to Bell's staging criteria (fixed/unchanging bowel loops, pneumatosis intestinalis, portal venous gas, pneumoperitoneum),

Objectives	Endpoints
	OR ○ Pneumatosis intestinalis, bowel necrosis, or perforation noted at surgery • Sepsis based on positive blood culture with clinical features of sepsis • Meningitis based on positive results for cerebrospinal fluid culture performed as part of infection workup • Retinopathy of prematurity ○ Confirmed by an ophthalmologist based on international committee Stage 4 or 5, OR ○ Requiring surgical treatment with laser or other surgical intervention including cryotherapy or treatment with antivascular endothelial growth factor • Intraventricular hemorrhage (IVH) ○ Grade 3 or 4 (severe IVH), OR ○ Any grade of IVH with posthemorrhagic hydrocephalus requiring a shunt • White matter injury, documented on cranial ultrasound or magnetic resonance imaging, as indicated by the following: ○ Multiple cystic lucencies in periventricular white matter (may be bilateral or unilateral, may vary in size, and be diffuse or focal in distribution), OR ○ Porencephalic cyst (not including subependymal or choroid plexus cysts), OR ○ Persistent ventriculomegaly, moderate to severe • Cerebellar hemorrhage (unilateral or bilateral)
	Supportive Key Secondary
	• Time to delivery • Proportion of births prior to $37^{0/7}$ weeks' gestation • Proportion of births at term ($37^{0/7}$ to $41^{6/7}$ weeks' gestation) • Length of neonatal hospital stay

Objectives	Endpoints
	Supportive Other Secondary
	• Proportion of births prior to $32^{0/7}$ weeks' gestation • Proportion of births prior to $28^{0/7}$ weeks' gestation • Proportion of births ≤7 days • Proportion of births ≤48 hours • Proportion of births ≤24 hours • Proportion of neonates with any of the co-primary composite neonatal morbidity and mortality, excluding RDS • Proportion of neonates with each individual component of the composite neonatal morbidity and mortality endpoints • Neonatal admission to a specialized care unit and length of stay • Newborn hospital readmission and length of stay • Ambulatory surgery • Time to treatment failure • Proportion of women receiving any putative tocolytic • Proportion of women experiencing subsequent episodes of preterm labor
Secondary	

• To describe the maternal, fetal, and neonatal safety profile during and after IV retosiban treatment compared with placebo	**Maternal:**
	• Incidence of reported AEs and serious AEs (SAEs)
	• Significant changes in vital signs and clinical laboratory tests
	• Incidence of clinical and laboratory toxicities causing subject to discontinue study treatment
	• Incidence of women scoring 12 or higher on the Edinburgh Postnatal Depression Scale (EPDS)
	• Maternal AEs of special interest
	  • Maternal death
	  • Chorioamnionitis and its complications
	  ○ Clinical chorioamnionitis, preterm premature rupture of membranes, endomyometritis, wound infection, pelvic abscess, bacteremia, septic shock, disseminated intravascular coagulation, and adult RDS

Objectives	Endpoints

	• Placental abruption
	• Postpartum hemorrhage – postpartum hemorrhage and/or retained placenta
	• Pulmonary edema
	Fetal:
	• Incidence of reported AEs and SAEs
	• Fetal acidosis
	• Fetal AEs of special interest
	  • Intrauterine fetal demise
	  • Category II or III fetal heart rate tracing (defined according to ACOG Practice Bulletin 106 [ACOG Practice Bulletin No. 106, 2009])
	  • Fetal inflammatory response syndrome characterized by cord blood interleukin-6 >11 pg/mL, funisitis, or chorionic vasculitis
	Neonatal:
	NOTE: Information collected from the time of birth through 28 days post EDD.
	• Neonatal Apgar scores (at 1 and 5 minutes after birth),
	• Growth parameters (weight, length, and head circumference) at birth and at discharge
	• Incidence of reported AEs and SAEs
	• Neonatal AEs of special interest will include the following:
	  • Neonatal death
	  • Asphyxia
	  • Infections (early onset neonatal sepsis, septic shock, pneumonia, meningitis)
	  • RDS
	  • Hypotension
	  • IVH/periventricular leukomalacia
	  • Bronchopulmonary dysplasia
	  • Neonatal acidosis
	  • Hyperbilirubinemia
	  • Necrotizing enterocolitis
	  • Hypoxic ischemic encephalopathy

Objectives	Endpoints

• To determine the effect of retosiban treatment compared with placebo on health care resource use for the maternal and neonatal hospitalizations	• Assess maternal and neonatal health care resource use associated with preterm labor and preterm delivery. Health care resource use of interest include:
	  • Maternal hospital admission (e.g., length of stay by hospital unit and type) and resource use (e.g., use of transport services and admission to extended stay facility)
	  • Neonatal interventions of interest (e.g., parenteral nutrition, surfactants, blood products), procedures (e.g., imaging, such as ultrasound and computed tomography), and surgical procedures
	  • Neonatal hospital admission (e.g., length of stay by hospital unit and type) and resource use (e.g., use associated with neonatal comorbidities of interest).

• To obtain further data on the pharmacokinetics of retosiban in pregnant women, including the effect of covariates such as age, weight, race/ethnicity, and GA on retosiban clearance and volume of distribution	• Retosiban clearance and volume of distribution and the effect of covariates on these parameters

4. STUDY DESIGN

4.1. Overall Design

NEWBORN-1 is a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. This study will be conducted in approximately 900 females, aged 12 to 45 years, with an uncomplicated, singleton pregnancy and intact membranes in preterm labor between $24^{0/7}$ and $33^{6/7}$ weeks of gestation. Eligible subjects (for the purposes of this protocol, subject refers to the mother and not the infant unless otherwise stated) will be randomly assigned in a 1:1 ratio to receive either retosiban IV infusion over 48 hours or matched placebo IV infusion over 48 hours (approximately 450 subjects in each group).

If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours. A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least 7 days prior to study enrollment. Investigators have discretion to use a standardized regimen of magnesium sulfate, as well as intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection (for additional details see Section 6.12).

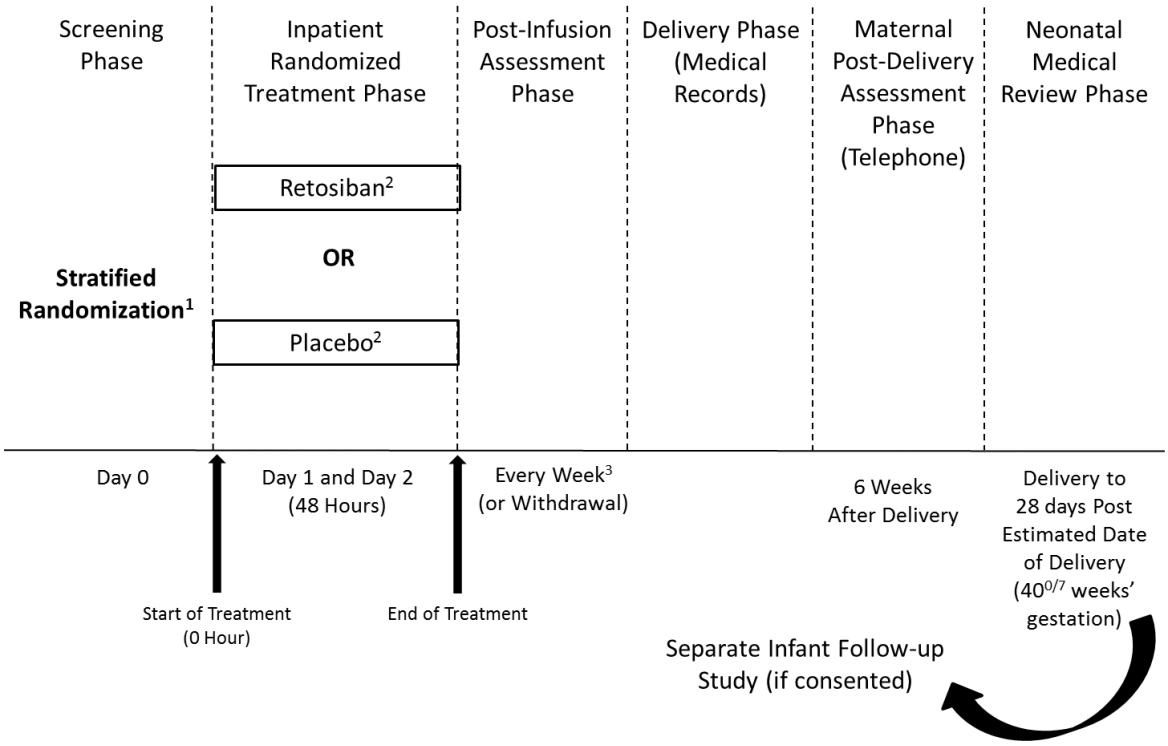
Prior to randomization, each subject will be stratified by progesterone treatment and GA. The progesterone strata will consist of subjects on established progesterone therapy or subjects not on established progesterone therapy at Screening (see Section 6.12.1.3 for details). The GA strata are $24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$, or $31^{0/7}$ to $33^{6/7}$.

All subjects exposed to randomized treatment will be asked to remain in the study through delivery and maternal post-delivery assessments and review of the newborn records. Withdrawal from the study should only occur if a subject either refuses to continue participation or is lost to follow-up (see Section 5.3.1).

4.2. Treatment Arms and Duration

NEWBORN-1 will comprise 6 phases: Screening, Inpatient Randomized Treatment, Post-Infusion Assessment, Delivery, Maternal Post-Delivery Assessment, and Neonatal Medical Review (Figure 2). The duration of any subject's (maternal or neonatal) participation in the study will be variable and dependent on GA at study entry and the date of delivery.

Figure 2 Study Design



1 Stratification (1:1) to retosiban or matched placebo based on established progesterone therapy at Screening (subjects on established progesterone therapy versus subjects not on established progesterone therapy) and gestational age ($24^{0/7}$ to $25^{6/7}$; $26^{0/7}$ to $27^{6/7}$; $28^{0/7}$ to $30^{6/7}$; $31^{0/7}$ to $33^{6/7}$).

2 If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours. A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least 7 days prior to study enrollment. Investigators have discretion to use a standardized regimen of magnesium sulfate, as well as intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection.

3 Subjects who have not delivered after 48 hours will return for a face-to-face post-infusion visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) after the Inpatient Randomized Treatment Phase. The subject will then be contacted every week via telephone to determine and record if she has delivered or if she has experienced any subsequent episodes of preterm labor. Retreatment with the investigational product (retosiban or placebo) is not allowed.

Each investigational site will have an obstetrician with expertise in high-risk obstetrics as the principal investigator who will be responsible for treatment, care, and review of data for the mother during the study and a neonatologist as a subinvestigator who will review the newborn hospital records to track and record the neonatal information.

Potential subjects who are thought to meet the eligibility criteria for the study will be informed of the requirements of the study and will give their written informed consent to participate in the study.

The Screening Phase will occur on Day 0, and assessments will primarily focus on maternal and fetal safety evaluations prior to dosing. The screening assessments must include a formal review of medical and obstetric history and a review of all eligibility requirements for the study.

Subjects will be randomly assigned to treatment on Day 1 of the Inpatient Randomized Treatment Phase. The treatment phase will be 48 hours. Retosiban treatment will be administered as a 6-mg IV loading dose over 5 minutes followed by a 6-mg/hour continuous infusion for the remainder of the 48-hour treatment period. The placebo control will be a normal saline (0.9% sodium chloride [NaCl]) infusion matched for the retosiban volume, IV loading dose over 5 minutes, and continuous infusion rate for the remainder of the 48-hour treatment period. The duration of the treatment should not exceed 48 hours.

An adequate response is based on (1) a clinically relevant reduction of contraction frequency and/or intensity or (2) no change in the cervical examination. Subjects with an inadequate response any time after the first hour of treatment will be administered another 6-mg retosiban or matched placebo loading dose and the retosiban or matched placebo infusion rate will be increased to 12 mg/hour for the remainder of the 48-hour treatment period. A subject's response should be assessed for at least 1 hour following a dose increase before a decision is made to discontinue randomized treatment due to lack of response. Investigators will be required to indicate in the electronic case report form (eCRF) the reason or reasons for a dose increase.

Treatment can be discontinued due to labor progression with imminent delivery, intolerance to treatment, and any contraindication to continuation of randomized treatment. Subjects who discontinue randomized treatment will be asked to remain in the study through the maternal post-delivery assessment and review of the newborn records. Withdrawal from the study should only occur if a subject either refuses to continue or is lost to follow-up.

Subjects who remain undelivered after 48 hours will be scheduled for a face-to-face post-infusion visit for obstetric assessments as part of the Post-Infusion Assessment Phase. The visit will be scheduled 1 week (acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase. The subject will then be contacted every week via telephone to determine and record if she has delivered or if she has experienced any subsequent episodes of preterm labor. Retreatment with the investigational product (IP; retosiban or placebo) is not allowed.

Once delivery is confirmed during the Delivery Phase of the study, the maternal delivery and hospitalization record will be reviewed for data collection by the investigator obstetrician. If delivery occurs at a different hospital, the investigator obstetrician will need to obtain the maternal delivery and hospitalization record for review. For those subjects who deliver at the investigative center within 12 hours of IP (retosiban or placebo) completion or discontinuation, a cord blood sample will be collected for pharmacokinetic (PK) analysis, and, if required, a corresponding maternal blood sample will be collected for PK analysis (see Section 7.6.1). Likewise, a breast milk/colostrum

sample will be collected for PK analysis in women who deliver at the investigative center and produce breast milk within 12 hours after IP completion or discontinuation.

During the Maternal Post-Delivery Assessment Phase, the subject will be contacted by telephone within 6 weeks of delivery for a post-delivery assessment, including an assessment of AEs (±2 weeks), status of breastfeeding (±2 weeks), and completion of the EPDS (-2 weeks/+6 weeks).

During the Neonatal Medical Review Phase, the neonatologist subinvestigator will conduct a comprehensive review of the newborn's medical records from delivery through 28 days EDD ($40^{0/7}$ weeks' gestation) for all subjects.

During the course of the study, the subject or other legal guardian for the infant will also be asked to consent to participate in a long-term study to follow infants for safety and neurodevelopment outcomes. The consenting process for the infant follow-up study can occur at any time during the study that is appropriate and convenient for the subject or legal guardian, such as during the Inpatient Randomized Treatment Phase or at the post-infusion assessment visit.

Detailed summaries of the assessments for each study phase are provided in the Study Procedures Manual (SPM).

Two interim analyses are planned. The first interim analysis will occur after approximately 150 subjects have completed delivery and have time-to-delivery results available. The second interim analysis will occur after approximately 400 women/newborn pairs are followed up to 28 days post EDD. At each interim analysis, all available safety and efficacy data will be reviewed by the unblinded independent data monitoring committee (IDMC) who may make recommendations to terminate the study based on prespecified criteria. Additionally, the IDMC may make recommendations to terminate the study at any time for an unfavorable benefit:risk profile. Subjects will continue to be enrolled while the interim analyses are being conducted.

Retosiban will not be available for compassionate use and will only be available as randomized treatment in this study.

4.3. Type and Number of Subjects

The study population is women aged 12 to 45 years with an uncomplicated singleton pregnancy in preterm labor with intact membranes between $24^{0/7}$ and $33^{6/7}$ weeks' gestation. Approximately 900 women (450 per treatment group) will be randomly assigned to ensure that approximately 800 women/newborns have recorded birth data (assumes ~10% missing data).

Italian Subjects: In Italy, the age restriction for study enrollment is 18 to 45 years.

4.4. Design Justification

As discussed in Section 2, there is no convincing evidence that current tocolytic regimens sufficiently prolong pregnancy to provide neonatal benefit beyond that of antenatal corticosteroids alone. In contrast, results from a Phase II placebo-controlled study suggest that retosiban's effect to prolong pregnancy may be sufficient to improve neonatal outcomes. In women with spontaneous preterm labor between $30^{0/7}$ to $35^{6/7}$ weeks' gestation, retosiban administered intravenously over 48 hours increased time to delivery by a mean of 8.2 days above and beyond that of placebo; this difference was consistent across GAs. Further, there is general agreement that prolonging the average time to delivery by 1 week in the absence of significant risk is likely to benefit the newborn, particularly in women who present in spontaneous preterm labor at early GAs. Together, these findings form the basis of the clinical hypothesis, which states that retosiban provides neonatal benefit beyond that of antenatal corticosteroids by prolonging pregnancy sufficiently to allow for continuing fetal maturation without causing significant risk to the fetus or neonate. To test this hypothesis, the study uses a randomized design that compares retosiban with placebo.

Placebo-controlled studies provide scientific rigor through their effect to distinguish an effective treatment from an ineffective treatment by controlling for all potential influences on the actual or apparent course of the disease or condition other than those arising from the pharmacologic action of the test drug. Such influences include the natural history of the disease or condition, subject or investigator expectations, use of other therapy, and subjective elements of diagnosis or assessment.

The study population represents a particularly vulnerable group for poor infant outcomes, for whom effective treatment options are limited. As a result, the protocol allows for the use of antenatal corticosteroids, either betamethasone or dexamethasone, magnesium sulfate in a standardized regimen, and intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection.

To fulfill regulatory requirements to study pediatric subjects, pregnant adolescents aged 12 to 17 years are allowed to participate in this study, with the exception of sites in Italy, where pregnant adolescents are not eligible to enroll in the study (see Section 5.1). Adolescent pregnancy is complicated by a higher likelihood of preterm labor and subsequent delivery, but there is no evidence that the pathophysiology of spontaneous labor and delivery differs between pregnant adolescents and adults or that the clinical course differs. Pregnant adolescents are more likely to deliver a low birth weight or preterm infant than older females (<40 years), and their babies have a higher risk of dying during infancy [Mathews, 2010; Martin, 2012]. Since local laws, customs, and institutional practice vary globally, investigator discretion in the enrollment of pediatric subjects is permitted.

4.5. Dose Justification

4.5.1. Retosiban

Retosiban will be administered as a 6-mg IV loading dose over 5 minutes followed by a 6-mg/hour continuous infusion for 48 hours. An adequate response is based on (1) a

clinically relevant reduction of contraction frequency and/or intensity or (2) no change in the cervical examination. For subjects with an inadequate response any time after the first hour of treatment, investigators should administer another 6-mg loading dose and increase the infusion rate to 12 mg/hour for the remainder of the 48-hour treatment period (see Section 6.1 and Section 6.3 for IP administration and dose adjustments, respectively).

The proposed retosiban dosing regimen has been informed primarily by results from the Phase II study (OTA105256) where a wide range of doses was evaluated in women with preterm labor. In Parts A and B of this Phase II study, the retosiban regimen was designed to yield a target concentration range based on preclinical models of preterm labor. Based on interim analysis of Parts A and B, the target mean steady-state concentration was refined in Part C to 75 ng/mL. The option to double the dose after 1 hour allows for between-subject variability in retosiban pharmacokinetics, receptor density, and half-maximal inhibitory concentration (IC50) values. Findings from Study OTA105256 Part C indicate this dosing strategy was successful, as 60% of subjects responded to the 6-mg/hour infusion, whereas 40% of subjects required an increase in the infusion rate to 12 mg/hour. These findings also support the initial 6-mg/hour infusion rate as the lowest effective dose for the majority of subjects, while recognizing that the higher 12-mg/hour infusion rate may be required in subjects failing to respond to the initial infusion rate.

Although a "highest–tolerated dose" strategy was not employed in selecting the retosiban dosing regimen, the retosiban infusion was well tolerated by pregnant women during the Phase II study, OTA105256. Moreover, there was no evidence for maternal, fetal, or neonatal toxicity. Pharmacokinetic simulations indicate that the Phase III dosing regimen will likely yield steady-state concentrations in the range of 50 to 388 ng/mL at 2 hours after starting retosiban treatment and decreasing to 8.9 to 128 ng/mL at 48 hours. These exposures are significantly less than those studied in the Phase I program, where retosiban doses were well tolerated [GlaxoSmithKline Document Number CM2006/00201/05].

Retosiban is primarily metabolized by the cytochrome P450 3A4 enzyme (CYP3A4). Drug-drug interaction studies indicate retosiban exposure is increased approximately 9-fold during co-administration of the strong CYP3A4 inhibitor ketoconazole, whereas concomitant administration of the strong CYP3A4 inducer efavirenz decreased retosiban exposure by 30%. As a result, the retosiban dosing regimen requires adjustment in subjects treated concomitantly with drugs that are strong CYP3A4 inhibitors or CYP3A4 inducers in order to achieve therapeutic retosiban concentrations. Refer to Section 6.3.2 for a description of the adjustments to the retosiban loading dose and infusion rate during co-administration with strong CYP3A4 inhibitors or CYP3A4 inducers.

4.5.2. Matched Placebo

Normal saline 0.9% NaCl administered intravenously will serve as the placebo control. The normal saline infusion will be matched for the retosiban volume, IV loading dose over 5 minutes, and continuous infusion rate, including a dose increase in subjects with

an inadequate response any time after the first hour of treatment (see Section 6.1 and Section 6.3 for IP administration and dose adjustments, respectively).

As discussed in Section 4.4, use of a placebo control serves to distinguish an effective treatment from an ineffective treatment by controlling for all potential influences on the actual or apparent course of preterm labor other than those arising from the pharmacologic effect of retosiban.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and nonclinical studies conducted with GSK221149 can be found in the IB. Table 1 and Table 2 outline the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Table 1 Potential Risks of Clinical Significance

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Fetal exposure through placental transfer	Retosiban is a substrate of P-gp and BCRP transporters, which are thought to play a role in keeping xenobiotics out of the CNS and out of the fetal blood. The preclinical data indicate very minimal, if any, maternal CNS penetration or placental transfer of retosiban as supported by: • In pregnant monkeys, there was no detectable retosiban in the cord blood when mothers were dosed up to 100 mg/kg (~7-fold human exposure). However, approximately 4% of circulating drug was detected in the cord blood when mothers were dosed at 300 mg/kg (~24-fold human exposure). • In reproductive toxicology studies in monkeys, where retosiban was given to pregnant monkeys, there were no adverse mother or infant behavioral, locomotor effects observed that were suggestive of CNS toxicity. • In rodent neurobehavioral safety studies, there were no adverse clinical signs observed at doses up to 1000 mg/kg. Adverse events and serious AEs reported in retosiban clinical trials to date have not indicated that retosiban has access to the maternal or fetal CNS; however, this has not been rigorously investigated. The short half-life of retosiban (~2 hours) is expected to minimize any significant risk.	Maternal blood and cord blood samples will be analyzed for levels of retosiban in women who deliver at an investigative center within 12 hours of the completion or discontinuation of the study infusion. Infants exposed to retosiban in utero will be followed for a minimum of 5 years in a separate follow-up study to assess overall safety and neurodevelopmental outcomes. Unblinded safety data will be monitored by an IDMC.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Neonatal exposure via breast milk	There were no effects on offspring growth and development in monkey reproductive toxicology studies, where systemic exposure to retosiban reached 14-fold the maximum clinical exposures. These findings suggest that exposure to retosiban during pregnancy had no adverse effect on breast milk or feeding. While there are no clinical data on the degree of retosiban transfer into breast milk, the available data based on physiochemical properties suggest retosiban will be excreted into breast milk if dosed close to or during the time of milk production. Given the rapid clearance of retosiban, the risk for neonatal drug exposure via breast milk appears low but could occur in the situation where the infant is fed breast milk/colostrum produced within 12 hours of the end of the infusion. Since lactogenesis is typically delayed 30 to 48 hours postpartum in mothers going to term (and is further delayed in mothers who deliver preterm), it seems unlikely that any drug would be in the plasma postpartum to transfer into the milk.	Breast milk/colostrum samples will be collected for measurement of retosiban when delivery occurs and lactation has started within 12 hours of receiving study treatment infusion. • When breast milk/colostrum is produced prior to 4 hours of the completion or discontinuation of the study treatment, a sample will be collected for evaluation, and consumption by the baby is not permitted. • When breast milk/colostrum is produced between 4 and 12 hours of the completion or discontinuation of the study treatment, a sample will be collected for evaluation, and the remainder of the breast milk can be consumed if the potential benefits to the infant are believed to outweigh the potential risks. The subject should be advised on the potential risks associated with feeding the infant her breast milk/colostrum that was expressed within 12 hours of the completion or discontinuation of the study treatment. • When breast milk is produced more than 12 hours after the completion or discontinuation of study treatment, no samples will be collected for evaluation and there will be no restrictions on consumption, given that this time frame is beyond 5 half-lives of retosiban. Safety monitoring for signals indicating adverse effects in infants following exposure to retosiban via breastfeeding will be performed throughout the study. Unblinded safety data will be monitored by an IDMC, including infants exposed to retosiban via breastfeeding.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Uterine atony and postpartum hemorrhage due to oxytocin receptor antagonism	Retosiban is a competitive oxytocin antagonist whose effects can be reversed by oxytocin agonists. Retosiban has a short elimination half-life (approximately 2 hours) and is rapidly removed from the body. Given the rapid clearance of retosiban, the risk for uterine atony appears low and would most likely occur in the situation where delivery occurs within 24 hours of treatment. The available clinical data for other oxytocin antagonists suggest the adverse effects of atony and postpartum hemorrhage are limited [Valenzuela, 1995; Thornton, 2009]. In monkey reproductive toxicology studies, where retosiban systemic exposure reached up to 14-fold of the maximum clinical exposures, there were no observations of postpartum hemorrhage. However, all monkey infants whose mothers received retosiban were born about 4 to 5 days after end of dosing. During the Phase II Study, OTA105256, 2 cases of postpartum hemorrhage were reported in subjects treated with retosiban. Both cases had confounding circumstances, as follows: One event occurred <48 hours from drug discontinuation and 2 hours after delivery in a subject with a prior history of retained placenta in a previous 23-week preterm delivery of twins. A history of retained placenta is a known risk factor for recurrent retained placenta [Stones, 1993; Endler, 2012]. The other event occurred >30 days after discontinuation of retosiban. The incidence of primary PPH (within 24 hours of delivery) is estimated to be between 4% to 6% of mothers who delivered [ACOG Practice Bulletin No. 76, 2006].	Given the rapid clearance of retosiban, the risk for uterine atony appears low and would most likely occur in the situation where delivery occurs within 24 hours of treatment. Investigators will be advised to refer to practice guidelines for treatment and/or management of postpartum hemorrhage, using agents approved for postpartum hemorrhage. These include oxytocin agonists and prostaglandin analogs. Retained placenta and PPH are AEs of special interest requiring the collection/assessment of risk factors for PPH, eCRFs for any event of PPH, and clinical parameters related to PPH. Evaluations will include outcomes such as time from delivery to expulsion of placenta and estimated blood loss. Unblinded safety data will be monitored by an IDMC.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Adverse maternal, fetal, or neonatal outcomes due to prolonging pregnancy in the presence of subclinical intrauterine infection	The study population includes women, particularly those presenting in labor prior to $30^{0/7}$ weeks of gestation, in whom intrauterine infection is implicated as a major etiologic factor. Infection may be chronic and asymptomatic with the first indication being preterm labor or rupture of the membranes. The asymptomatic nature of intrauterine infection, including lack of fever, abdominal pain, and fetal tachycardia, makes the diagnosis challenging. Infection is thought to trigger the labor process as a protective means for both the mother and baby [Goldenberg, 2002].	The protocol will exclude women with a temperature >100.4°F (38°C) for more than 1 hour or ≥101°F (38.3°C), as well as women with confirmed or suspected contraindication for continuation of pregnancy, such as chorioamnionitis, premature rupture of membranes, and abruption. Placental tissue samples will be collected in study 200721 (ZINN) when delivery occurs at an investigative center to examine safety and efficacy outcomes in subjects with subclinical intrauterine infection. A set of AEs of special interest identified in the literature as linked to maternal clinical or subclinical infection has been generated and will be used to collect targeted information of these AEs. This information will be monitored in stream by an IDMC. The unblinded IDMC will review all available safety and efficacy data.
Potential drug-drug interaction with inhibitors of BCRP or P-gp	Retosiban is a substrate of murine BCRP and P-gp *in vitro*. Inhibitors of BCRP and P-gp have the potential to increase exposure of retosiban when co-administered. BCRP and P-gp is expressed in placental membranes and the blood-brain barrier, and there is the potential of increased maternal CNS and fetal exposure to retosiban when co-administered with inhibitors. Clinical experience with exposures 10-fold higher than the exposure at the planned therapeutic dose has shown retosiban to be safe and well tolerated, with no observed untoward effects in adult women of childbearing potential.	Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure. The impact of concomitant use of retosiban with inhibitors of BCRP or P-gp will be assessed through AE monitoring. Analysis of maternal serum and cord blood samples will be performed when delivery occurs within 12 hours of study treatment infusion with co-administration of a BCRP or P-gp inhibitor to assess the effect of P-gp inhibition on placental transfer of retosiban.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Potential drug-drug interaction: Increased exposure of retosiban when co-administered with inhibitors of CYP3A4	In a clinical study with healthy subjects, co-administration of retosiban with ketoconazole (a strong CYP3A4 inhibitor) increased the Cmax and AUC of retosiban, 5.2- and 8.7-fold, respectively.	Administration of strong CYP3A4 inhibitors concomitantly with IP requires an adjustment to the retosiban dosing regimen (see Section 6.3.2 and the IB). Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure.
Potential drug-drug interaction: Decreased exposure of retosiban when co-administered with inducers of CYP3A4	In healthy, nonpregnant females, co-administration of intravenous retosiban with efavirenz (a moderate CYP3A4 inducer) increased the clearance of retosiban by 42% and reduced total exposure by 30% and peak exposure by about 20%.	Administration of strong CYP3A4 inducer concomitantly with IP requires an adjustment to the retosiban dosing regimen (see Section 6.3.2 and the IB). Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure.
Potential decreased therapeutic effect of drugs metabolized by CYP3A4 when co-administered with retosiban	Evidence of metabolic auto-induction has been observed with repeat intravenous dosing of retosiban in women with preterm labor, as well as in healthy nonpregnant women given repeat oral doses of retosiban over 2 weeks.	As 48-hour administration of retosiban has the potential to increase the rate of metabolism of drugs metabolized by CYP3A4, it is recommended that these drugs be monitored for a decrease in their therapeutic effect. Details are provided in the IB. Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure.

AE = adverse event; AUC = area under the plasma concentration time curve; BCRP = breast cancer resistance protein; Cmax = maximum plasma concentration; CNS = central nervous system; eCRF = electronic case report form; CYP3A4 = cytochrome P450 3A4 enzyme; IB = investigator's brochure; IDMC = independent data monitoring committee; P-gp = P-glycoprotein; PPH = postpartum hemorrhage.

Table 2 Potential Safety Concerns

Potential Safety Concern	Summary of Data/Rationale for Concern	Mitigation Strategy
Pulmonary edema	Pulmonary edema is a rare but potentially life-threatening complication of pregnancy. In the setting of preterm labor, pulmonary edema is thought to involve both increased hydrostatic pressure and altered vascular permeability. Factors associated with pulmonary edema include spontaneous preterm labor, multifetal pregnancy, chorioamnionitis, pre-eclampsia, cardiac disease, fluid overload, blood transfusion, corticosteroid therapy, and tocolytic treatment. Magnesium sulfate is implicated especially when additional risk factors are present. Randomized studies have not shown an increased risk of pulmonary edema or other serious maternal complications with antenatal magnesium sulfate [Doyle, 2009; Conde-Agudelo, 2009; Bain, 2013]. A retrospective chart review showed that contributing factors for pulmonary edema during magnesium sulfate treatment included high dose, high infusion rate, high net positive fluid balance, concomitant tocolysis, and multifetal gestations [Samol, 2005].	Women with identified risk factors for pulmonary edema are excluded from the clinical study. These include multifetal pregnancies, pre-eclampsia, chorioamnionitis, and certain pre-existing cardiovascular conditions. Combination administration of a tocolytic is not permitted in the clinical studies. Maintenance tocolysis is not allowed. Guidance is provided to investigators regarding monitoring fluid intake and output up to the time of starting treatment and for the duration of treatment (see Section 7.4.8). Pulmonary edema is designated as an AE of special interest requiring the collection and/or assessment of specific, relevant history and physical examination findings, targeted eCRFs to characterize any reported events, and a maximum duration of tocolytic treatment with magnesium sulfate of 48 hours.

AE = adverse event; eCRF = electronic case report form.

4.6.2. Benefit Assessment

Birth prior to 34 weeks' gestation represents roughly 30% of preterm births in the United States, half of which are preceded by spontaneous labor [Martin, 2012; Tucker, 1991; Berkowitz, 1998; Meis, 1998; Goldenberg, 2008]. Premature birth in this group carries a disproportionately high risk for death, neonatal complications, and long-term disabilities. Infants born prior to 32 weeks' gestation die at a rate 72 times that of term infants; the mortality rate for infants born between 32 and 33 weeks' gestation is 7-fold higher [Mathews, 2010]. Surviving infants remain susceptible to both short-term and long-term prematurity complications, resulting from injury to immature organ systems [Stoll, 2010; Saigal, 2008].

Unfortunately, neonatal mortality and morbidity remain disproportionately high in the study population despite the proven benefit of antenatal corticosteroids. Therefore, if the retosiban program confirms the clinical hypothesis, it would provide the first compelling and unambiguous evidence that a therapeutic intervention during spontaneous preterm labor can prolong pregnancy sufficiently to reduce the risk for prematurity complications beyond that of antenatal corticosteroids.

4.6.3. Overall Benefit:Risk Conclusion

Based on the Phase II results showing retosiban treatment significantly increased the time to delivery and reduced preterm births, this study will test whether retosiban can provide neonatal benefit by prolonging pregnancy and allowing for continued maturation of fetal organs and systems.

Although experience in pregnant women is limited, the retosiban safety profile is favorable, and no clinical or preclinical safety issues have been identified that preclude further development. In addition, the protocol institutes a number of measures aimed at mitigating potential risks to subjects participating in the study. These include extensive maternal, fetal, and neonatal safety assessments and an IDMC to monitor maternal, fetal, and neonatal safety in an ongoing manner throughout the study.

Balancing the potential risks of retosiban treatment against the anticipated benefits afforded to subjects with preterm labor, the overall benefit:risk assessment of retosiban appears reasonable for the mother, fetus, and infant.

For detailed information on the identified risks and risk-benefit assessment of retosiban, refer to the IB [GlaxoSmithKline Document Number CM2006/00201/05].

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GlaxoSmithKline (GSK) IP or other study treatment that may affect subject eligibility is provided in the IB and other pertinent documents [GlaxoSmithKline Document Number CM2006/00201/05].

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Signed and dated written informed consent is required prior to a subject's participation in the study and the performance of any protocol-specific procedures. At sites where enrollment of adolescents is allowed, adolescents aged 12 to 17 years must provide written agreement to participate in the study in accordance with applicable regulatory and country or state requirements. Subjects will also be asked to sign a release for medical records at the time of consenting to allow access to both the maternal and neonatal records including information about delivery and infant care as well as information collected prior to the consent having been signed

   NOTE: Prescreening alone does not necessarily require consent as this activity may be accomplished in the absence of study-specific procedures or assessments. In many cases, standard care and standard medical triage will provide sufficient information or evidence as to whether or not the subject is eligible for the study

2. Females aged 12 to 45 years, with an uncomplicated, singleton pregnancy and intact membranes in spontaneous preterm labor (NOTE: Since local laws, customs, and institutional practice vary globally, investigator discretion in the enrollment of pediatric subjects is permitted, except in Italy)

   Italian Subjects: In Italy, the age restriction for study enrollment is 18 to 45 years.

3. Gestational age between $24^{0/7}$ and $33^{6/7}$ weeks as determined by (1) known fertilization date, either *in vitro* fertilization or intrauterine insemination or (2) a best estimated due date confirmed or established by the earliest ultrasound performed before $24^{0/7}$ weeks gestation.

   In situations where prenatal ultrasound records are not available at the time the subject presents, the investigator may enroll the subject using the GA based on a verbal history from the subject with the intent of getting confirmation from the medical records or from the subject's primary care obstetrician as soon as possible.

4. Females must be diagnosed with preterm labor according to both of the following criteria (a and b):

   a. Regular uterine contractions, confirmed by tocodynamometry, at a rate of ≥4 contractions of at least 30 seconds' duration during a 30-minute interval. Where tocodynamometry is not technically feasible, assessment by manual palpation will be permitted and must be documented.

   AND

   b. At least 1 of the following:

      i. Cervical dilation ≥2 cm and ≤4 cm by digital cervical examination OR

      ii. If <2 cm dilation by the required initial digital cervical examination, a cervical change (2 examinations must be documented) consistent with 1 of the following:

         - An absolute increase of at least 25% effacement (e.g., a change in effacement from 50% to 75%) by digital examination or a 10-mm decrease in cervical length by transvaginal ultrasound

           OR

         - A 1-cm increase in cervical dilation by digital cervical examination

5. Current or past tocolytic treatment as follows:

   a. Subjects in whom tocolytic treatment has not been initiated prior to consent are eligible for the study

   b. Transferred or referred subjects for whom parenteral magnesium sulfate treatment has been started before Screening are eligible provided they meet all eligibility criteria

   c. Subjects receiving a prohibited tocolytic in this study are eligible only if the treatment is stopped before randomization and provided they meet all eligibility criteria

   d. Subjects with a historical failure of a tocolytic treatment in a previous episode of preterm labor during the current pregnancy are eligible provided they meet all eligibility criteria

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Fever with a temperature >100.4°F (38°C) for more than 1 hour or ≥101°F (38.3°C) in the 24 hours prior to the start of study treatment
2. Women with maternal-fetal conditions that potentially necessitate the need for delivery, such as pre-eclampsia or fetal compromise

3. A fetus with any diagnosis, condition, treatment, or other factor that in the opinion of the investigator has the potential to affect or confound assessments of efficacy or safety (e.g., nonreassuring fetal status, intrauterine growth restriction, major congenital anomaly)
4. Preterm premature rupture of membranes
5. Women with any confirmed or suspected contraindication to prolongation of pregnancy, such as placental abruption, chorioamnionitis, or placenta previa
6. Evidence of polyhydramnios (amniotic fluid index [AFI] >25 cm) or oligohydramnios (AFI <5 cm)
7. Women with co-morbid medical or obstetric conditions that in the opinion of the investigator have the potential to complicate the pregnancy course and outcomes, such as uncontrolled hypertension or uncontrolled diabetes (if known, history of glycosylated hemoglobin >8% at any time during pregnancy), known or suspected maternal Zika infection during gestation (see SPM for details), or compromise the safety of the subject, such as underlying cardiovascular disorder (specifically ischemic cardiac disease, congenital heart disease, pulmonary hypertension, valvular heart disease, arrhythmias, and cardiomyopathy)
8. Women with a history of substance abuse during the pregnancy or dependency that may have the potential to complicate the pregnancy outcome
9. Women with any diagnosis, condition, treatment, or other factor that, in the opinion of the investigator, has the potential to affect or confound assessments of efficacy or safety
10. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment)

    NOTES:

    - Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice, or cirrhosis
    - Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (or positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria
11. History of sensitivity to any of the IPs or components thereof or a history of drug or other allergy that, in the opinion of the investigator or PPD medical monitor, contraindicates the subject's participation

5.3. Withdrawal From Study, Discontinuation of IP, and Stopping Criteria

The section describes and distinguishes the following:

- Withdrawal of the subject from the study after randomization but before administration of IP (Section 5.3.1.1) and after administration of IP (Section 5.3.1.2)
- Discontinuation of the IP (Section 5.3.2), wherein subjects who receive but then discontinue from IP will not be considered withdrawn from the study and should remain in the study and continue to be followed for efficacy and safety.
- Specific stopping criteria before and during dosing, including liver function test criteria (Section 5.3.3) and QTc findings (Section 5.3.4).

5.3.1. Withdrawal From Study

5.3.1.1. Withdrawal From Study Participation After Randomization but Prior to Investigational Product Administration

Any subject with a nonreassuring fetal heart rate pattern, a re-assessment that determines tocolytic therapy is no longer indicated (according to investigator's medical discretion), abnormal levels of alanine aminotransferase (ALT) or bilirubin (if results are available), or a clinically significant abnormal finding on an electrocardiogram (ECG) cannot be dosed and will be withdrawn from the study. The reasons for not dosing a subject will be recorded in the eCRF and source documents. Subjects who are withdrawn prior to receiving randomized IP will not be followed.

A nonreassuring fetal heart rate is defined as either unresolved Category 3 tracings (including either [1] the absence of baseline fetal heart rate variability and any of the following: recurrent late decelerations, recurrent variable decelerations, or bradycardia; or [2] sinusoidal pattern) or at the investigator's discretion.

Sites Not in Italy: If local laboratory results are available before the start of dosing and reveal that ALT is ≥2 × the upper limit of normal (ULN) or total bilirubin is >1.5 × ULN (>35% direct bilirubin), the subject should not be dosed and should be withdrawn from the study. An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%.

With the exception of sites in Italy, dosing may be started before local liver function test results are available. If the local laboratory results reveal liver abnormalities as defined in Section 5.3.3 and Appendix 2, study drug treatment must be discontinued.

Sites in Italy: For sites located in Italy, dosing must not start before local laboratory liver function test results are obtained and reviewed by the investigator. If local laboratory liver function test results reveal that ALT is ≥2 × ULN or total bilirubin is >1.5 × ULN (>35% direct bilirubin), the subject must not be dosed and should be withdrawn from the study. An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%.

5.3.1.2. Withdrawal From Study Participation After Beginning Randomized Treatment

All subjects who are randomly assigned to and begin treatment (i.e., randomized treatment) should be encouraged to complete all phases of the study, including those who discontinue randomized treatment. However, a subject may voluntarily withdraw from study participation at any time or be withdrawn at any time at the discretion of the investigator for any maternal obstetrical or medical complications after consultation with the PPD medical monitor. If a subject withdraws from the study, no additional visits can occur or procedures performed, and the subject may request destruction of any samples taken; the investigator must document this request in the site study records.

Subjects who are withdrawn from study participation after starting randomized treatment will not be replaced. Reasons for study withdrawal will be recorded in the eCRF and the subject's source document. A subject may be withdrawn from the study for the following reasons:

- Lost to follow-up
- Subject voluntarily withdrew consent
- Investigator decision to withdraw the subject from participation; investigators must consult the PPD medical monitor before withdrawing a subject from participation in the study
- Termination of the study by GSK

Subjects who are withdrawn after starting the Inpatient Randomized Treatment Phase but before the Post-Infusion Assessment Phase will be asked to return and complete the assessments specified for the 1-week face-to-face post-infusion assessment visit before withdrawing from the study (Table 5).

Withdrawal from this study after beginning randomized treatment does not preclude involvement in the separate infant follow-up study.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study
- In cases where the subject is deemed "lost to follow-up," the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record

- Should the subject continue to be unreachable, only then will she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF

5.3.2. Discontinuation of Investigational Product

Subjects who receive but who discontinue from IP will not be considered withdrawn from the study and should remain in the study and continue to be followed for efficacy and safety. Once delivered, newborns will also continue to be followed for safety and outcomes through the 28 days post EDD.

A subject may voluntarily discontinue from the IP at any time. The investigator may also, at his or her discretion, discontinue the IP at any time for any medical reason or maternal or fetal complications. Subjects who discontinue randomized treatment will be managed by the investigator according to standard care.

Subjects who discontinue the IP will not be replaced. Reasons for discontinuation from IP will be recorded in the eCRF and the subject's source documents

A subject will also be discontinued from IP under the following circumstances:

1. Labor progression or delivery (vaginal or caesarean section) occurs during the Inpatient Randomized Treatment Phase
2. Intolerance of assigned treatment occurs during the Inpatient Randomized Treatment Phase
3. An obstetric indication for delivery (e.g., nonreassuring fetal status)
4. Contraindication for continuing randomized treatment including, but not limited to, infection (i.e., chorioamnionitis) or placental insufficiency as evidenced by, for example, abruptio placentae, intrauterine growth restriction, nonreassuring fetal status or death, severe pre-eclampsia/eclampsia, maternal bleeding with hemodynamic instability, or other conditions at the discretion of the investigator
5. Abnormal liver function test result (see Section 5.3.3)
6. An abnormal corrected QT interval (see Section 5.3.4)

Subjects discontinuing the IP for any of the above reasons can and should continue to receive antenatal corticosteroids (either betamethasone or dexamethasone) for fetal maturation if not yet completed and still clinically indicated.

Subjects discontinuing the IP who have not yet delivered will continue in the study through delivery, the maternal post-delivery assessment, and newborn record review. These subjects will be included in the Intent-to-Treat (ITT) and Safety Populations. Additionally, all infants should be consented for the separate infant follow-up study.

5.3.3. Liver Chemistry Stopping Criteria

Blood samples will be collected for central laboratory evaluation at Screening (prior to treatment), during Day 2 of the randomized treatment phase, and at the 1-week

face-to-face post-infusion assessment visit for additional liver function testing to ensure subject safety and to evaluate liver event etiology (in alignment with the US Food and Drug Administration premarketing clinical liver safety guidance); http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Sites Not in Italy: At Screening, before IP administration, ALT and bilirubin test results from a local laboratory should be obtained, although dosing may be started prior to the availability of these results. However, if the local laboratory results are available before the start of dosing and meet the following criteria, the subject should not be dosed and should be withdrawn from the study:

- ALT ≥2 × ULN OR total bilirubin >1.5 × ULN (>35% direct bilirubin). An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%.

Phase III-IV liver chemistry stopping criteria are presented in Figure 3 and Appendix 2.

The local and central laboratory liver function test results should be reviewed for the abnormalities shown in Figure 3. If the laboratory results are not available at the start of dosing and subsequent local OR central laboratory results are abnormal, dosing may be continued at the discretion of the investigator, as long as they do not exceed the liver chemistry stopping criteria shown in Figure 3 and detailed in Appendix 2.

Sites in Italy: At Screening, before IP administration, ALT and bilirubin test results from a local laboratory must be obtained and reviewed by the investigator. If the local laboratory liver function test results meet the following criteria, the subject must not be dosed and should be withdrawn from the study:

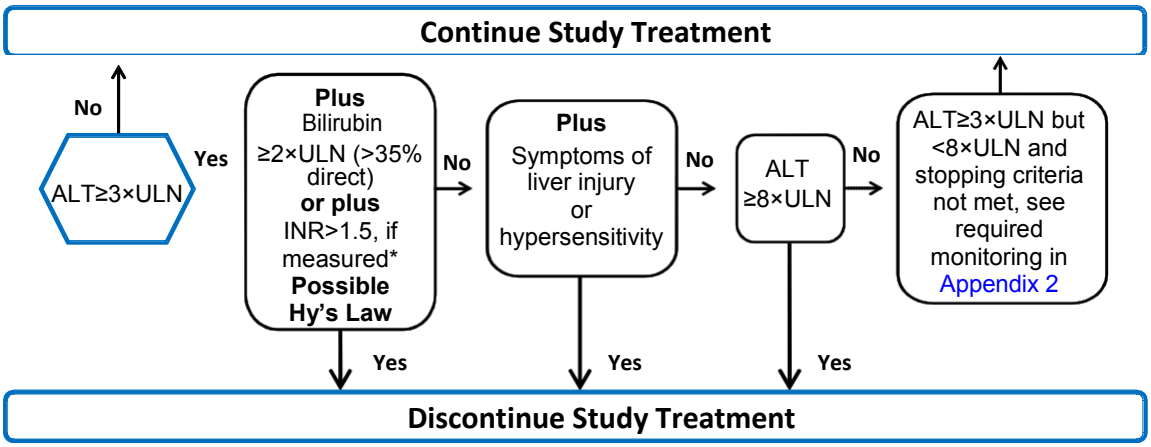
- ALT ≥2 × ULN OR total bilirubin >1.5 × ULN (>35% direct bilirubin). An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%.

Phase III-IV liver chemistry stopping criteria are presented in Figure 3 and Appendix 2.

The local and central laboratory liver function test results should be reviewed for the abnormalities shown in Figure 3. If after the start of dosing, the central laboratory results are abnormal, dosing may be continued at the discretion of the investigator, as long as they do not exceed the liver chemistry stopping criteria shown in Figure 3 and detailed in Appendix 2.

NOTE for All Sites: The central laboratory report will include results for ALT, aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and direct bilirubin.

Figure 3 Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



- **Must refer to Liver Safety Required Actions and Follow-up Assessments section in Appendix 2**
- **Report as an SAE if possible Hy's Law case:** ALT≥3×ULN and Bilirubin ≥2×ULN (>35% direct) or INR >1.5, if measured

*INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants

ALT = alanine aminotransferase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

The complete Liver Safety Required Actions and Follow-up Assessments section can be found in Appendix 2.

5.3.3.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.3.4. QTc Stopping Criteria

Should the subject require an ECG during the infusion and the results meet the following defined corrected QT interval (QTc) criteria, the IP will be discontinued:

- An abnormal QTc using the Fridericia formula (QTcF) detected during standard care of the subject based on the following criteria:
  - QTcF >500 msec or uncorrected QT >600 msec
  - Change from baseline QTcF value of >60 msec

For subjects with underlying **bundle branch block**, treatment should be discontinued in the following circumstances:

- QTcF >500 msec in a subject with a baseline QTcF value of <450 msec
- QTcF ≥530 msec in a subject with a baseline QTcF value between 450 and 480 msec
- The QTc should be based on single electrocardiogram

5.4. Subject and Study Completion

A completed subject is defined as one who has completed all phases of the study including the post-delivery assessment visit. Subjects who receive but who discontinue from IP will not be considered withdrawn from the study and should remain in the study and continue to be followed for efficacy and safety (see Section 5.3.2).

The end of the study is defined as the neonatal record review at 28 days post EDD for the last subject randomly assigned to and treated with IP.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term "study treatment" is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

Retosiban for IV administration will be supplied as solution for infusion, consisting of a clear colorless solution of retosiban at a concentration of 15 mg/mL in 56% vol/vol ethanol/acetate buffer concentrate. The solution is sterilized by filtration and aseptically filled into glass vials. The vials are sealed with rubber stoppers and aluminum seals with a plastic flip-off lid. Each single-use 5-mL vial contains 75 mg retosiban as solution for infusion (see Table 3).

The retosiban infusion will be prepared by an unblinded pharmacist or other qualified professional, using two 5 mL retosiban vials admixed in a 500 mL 0.9% NaCl infusion bag to obtain a concentration of 0.3 mg/mL (150 mg retosiban in 500 mL 0.9% NaCl). The infusion admixture is a clear, colorless solution.

An unblinded pharmacist or other qualified individual will prepare the placebo infusion using 0.9% NaCl 500 mL matched for the retosiban loading dose and continuous infusion rates, including a dose increase in subjects with an inadequate response any time after the first hour of treatment.

Table 3 summarizes the study treatments.

Table 3 Retosiban Investigational Product and Other Study Treatment

	Study Treatment	
Product Name	**Retosiban (GSK221149) Solution for Infusion**	**PTM IV Solution (0.9% NaCl)**
Drug product description	Clear, colorless solution for infusion in a 5-mL vial containing 75 mg of retosiban	A placebo-matched glass vial is not provided.
Unit dose strengths/ Dosage levels	Retosiban 15 mg/mL The total dose given over 48 hours should not exceed 300 mg at the 6-mg/hour infusion rate and 582 mg at the 12-mg/hour infusion rate.	0.9% NaCl matched for the retosiban loading dose and continuous infusion rates
Route of administration	IV	IV
Dosing instructions:	The retosiban 6-mg loading dose is administered at an infusion rate of 240 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 20 mL/hour to deliver retosiban at a rate of 6 mg/hour for the remainder of the 48-hour treatment period. For subjects with an inadequate response any time after the first hour of treatment, investigators should administer another 6-mg loading dose by increasing the infusion rate to 240 mL/hour for 5 minutes, after which the infusion rate is set to 40 mL/hour in order to deliver retosiban at a rate of 12 mg/hour. For subjects receiving concomitant treatment with a strong CYP3A4 inhibitor, the retosiban 3-mg loading dose is administered at an infusion rate of 120 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 6.7 mL/hour to deliver retosiban at a rate of 2 mg/hour. For subjects with an inadequate response any time after the first hour, an additional 1-mg loading dose is administered by increasing the infusion rate to 40 mL/hour over 5 minutes after which the infusion rate is set to 10 mL/hour to deliver retosiban at 3 mg/hour for the remainder of the 48-hour treatment period. For subjects receiving concomitant treatment with a strong CYP3A4 inducer, the retosiban 8.5-mg loading dose is administered at an infusion rate of 340 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 28 mL/hour to deliver retosiban at a rate of 8.5 mg/hour. For subjects with an inadequate response any time after the first hour, an additional 3.5-mg loading dose is administered by increasing the infusion rate to 140 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 40 mL/hour to deliver retosiban at a rate of 12 mg/hour. See the Study Pharmacy Manual for detailed instructions.	Intravenous administration of the 0.9% NaCl solution will be matched to the loading dose rate of 240 mL/hour for 5 minutes, after which the infusion rate is set to 20 mL/hour. For subjects with an inadequate response any time after the first hour of treatment, investigators should administer another loading dose by increasing the infusion rate to 240 mL/hour for 5 minutes, after which the infusion rate is set to 40 mL/hour. For subjects receiving concomitant treatment with a strong CYP3A4 inhibitor, the loading dose is administered at an infusion rate of 120 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 6.7 mL/hour. For patients with an inadequate response any time after the first hour, an additional loading dose is administered by increasing the infusion rate to 40 mL/hour over 5 minutes, after which the infusion rate is set to 10 mL/hour. For subjects receiving concomitant treatment with a strong CYP3A4 inducer, the loading dose is administered over 5 minutes at an infusion rate of 340 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 28 mL/hour. For patients with an inadequate response any time after the first hour, an additional loading dose is administered by increasing the infusion rate to 140 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 40 mL/hour. See Study Pharmacy Manual for detailed instructions.

Product Name	Study Treatment	
	Retosiban (GSK221149) Solution for Infusion	PTM IV Solution (0.9% NaCl)
Manufacturer/ Source of procurement	GSK	Not applicable – to be sourced locally

CYP3A4 = cytochrome P450 3A4 enzyme; IV = intravenous; GSK = GlaxoSmithKline; NaCl = sodium chloride; PTM = placebo to match.

6.2. Treatment Assignment

Subjects will be stratified by progesterone treatment and GA. The progesterone strata will consist of subjects on established progesterone therapy or subjects not on established progesterone therapy at Screening. The GA strata are $24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$, or $31^{0/7}$ to $33^{6/7}$. Subjects within each stratum will be randomly assigned in 1:1 ratio to receive either retosiban or placebo using an interactive voice response system (IVRS)/interactive web response system (IWRS) in accordance with the randomization schedule generated by PPD, prior to the start of the study, using validated internal software.

The retosiban and matching placebo regimen are described in Table 3. The IP will be administered by study personnel during each dosing session. Retreatment with the IP (retosiban or placebo) is not allowed. Temporary interruptions of the IP are permitted, and the reasons must be recorded in the eCRF (e.g., problems with IV line).

The time of dosing (i.e., start of the infusion) will be designated as time 0. All subsequent time points will be in relation to this time point. Information regarding IV administration, dosing adjustments, and admixture preparation can also be found in the SPM and Study Pharmacy Manual.

6.3. Subject-Specific Dose Adjustment Criteria

6.3.1. Inadequate Response

An adequate response is based on (1) a clinically relevant reduction of contraction frequency and/or intensity or (2) no change in the cervical examination. An inadequate response is defined as a clinically significant change in the cervical examination or no significant reduction in contraction frequency and/or intensity. For subjects with an inadequate response any time after the first hour of treatment with retosiban or matching placebo, investigators should administer another 6-mg loading dose by increasing the infusion rate to 240 mL/hour for 5 minutes, after which the infusion rate is set to 40 mL/hour in order to deliver retosiban at a rate of 12 mg/hour. Investigators will be required to indicate in the eCRF the reason or reasons for a dose increase. A subject's response should be assessed for at least 1 hour following a dose increase before a decision is made to discontinue randomized treatment due to an inadequate response.

See Section 5.3.2 for details regarding discontinuation of the IP.

6.3.2. Concurrent Administration of Investigational Product With Strong CYP3A4 Inhibitors or Strong CYP3A4 Inducers

Retosiban undergoes oxidative metabolism, primarily mediated by CYP3A4 (see Section 4.5.1). As a result, concomitant administration of drugs that are strong CYP3A4 inhibitors may result in increased exposure to retosiban. When given orally, retosiban exposure was increased 8.7-fold, as measured by area under the plasma concentration-time curve (AUC), in the presence of ketoconazole, a strong CYP3A4 inhibitor.

To achieve exposures similar to those achieved with the retosiban 6-mg/hour dosing regimen, retosiban should be administered as a 3-mg loading dose over 5 minutes followed by a 2-mg/hour continuous infusion in subjects who are being treated concomitantly with a strong CYP3A4 inhibitor (see Section 6.12.1.5). See Table 3 for additional dosing instructions.

For subjects chronically taking a drug known to be a strong CYP3A4 inducer, the initial dose of retosiban should be an 8.5-mg loading dose over 5 minutes followed by an 8.5-mg/hour continuous infusion for the remainder of the 48-hour treatment period (see Section 6.12.1.6). See Table 3 for additional dosing instructions.

See the Study Pharmacy Manual for detailed instructions. A list of strong, moderate, and weak CYP3A4 inhibitors and inducers is provided in Appendix 7.

6.4. Managing Dose Interruptions

Temporary interruptions of the IP are permitted. The following procedures should be followed in the event of a dose interruption:

- If the interruption is <60 minutes, restart the IP infusion.
- If the interruption is from 60 to 90 minutes, inclusive, administer a loading dose at a rate equal to one-half of the prior loading dose rate. For example, if the loading dose rate prior to the interruption was 240 mL/hour over 5 minutes, administer the loading dose at 120 mL/hour over 5 minutes, and then resume the infusion.
- If the interruption is >90 minutes, administer a loading dose at a rate equal to the prior loading dose rate. For example, if the prior loading dose was administered at 240 mL/hour over 5 minutes, administer the loading dose at 240 mL/hour over 5 minutes, and then resume the infusion.

Any changes in the dose rate, corresponding start and stop times, and the reason for an interruption must be recorded in the eCRF.

6.5. Blinding

The pharmacist or other qualified individual responsible for IP accountability, storage, and preparation will be unblinded, as will the PPD clinical research associate responsible for IP accountability. These personnel will maintain the integrity of the study blind. All other subjects and study personnel (i.e., investigators, GSK, PPD) will be blinded for the

duration of this study. Subjects (or parents/legal guardians of the neonate) will remain blinded throughout the duration of the separate long-term infant follow-up study.

The IDMC will review unblinded data periodically in addition to 2 formal interim analyses in accordance with the IDMC charter. Unblinded data will be provided by an independent statistical data analysis center.

This will be a double-blind study and the following will apply:

- The investigator or treating physician may unblind a subject's treatment assignment **in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment (refer to the PPD IVRS/IWRS Site User Guide for details).
- It is preferred (but not required) that the investigator first contact the PPD medical monitor to discuss options **before** unblinding the subject's treatment assignment.
- If PPD personnel are not contacted before the unblinding, the investigator must notify PPD as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study (refer to the SPM for details).
- The date and reason for the unblinding must be fully documented in the eCRF.
- A subject may continue in the study if that subject's treatment assignment is unblinded (refer to the SPM).
- GSK's Global Clinical Safety and Pharmacovigilance staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of the retosiban solution and the matching placebo are detailed in the Study Pharmacy Manual.

The following considerations must be made with regard to IP preparation, handling, storage, and accountability in this study:

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records)
- Further guidance and information for final disposition of unused study treatment are provided in the Study Pharmacy Manual
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, medical monitor, and/or GSK study contact
- A material safety data sheet or equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or will be made available upon request from GSK

6.8. Compliance With Study Treatment Administration

This study will be conducted under the direct supervision of the investigator obstetrician or his/her designees; IP will be administered under the supervision of study personnel and compliance will be monitored.

The exact start and stop times of the infusion should be recorded in the eCRF.

6.9. Treatment of Study Treatment Overdose

Any signs or symptoms of retosiban overdosage will be treated symptomatically. No specific antidote is known.

In the event of an overdose, the principal investigator should take the following actions:

1. Contact the medical monitor immediately
2. Closely monitor the subject for AEs or SAEs and laboratory abnormalities

3. Obtain a plasma sample for PK analysis within 12 hours from the time of the overdose if requested by the medical monitor (determined on a case-by-case basis)
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the subject.

6.10. Treatment After the End of the Study

The investigator is responsible for ensuring that consideration has been given to the poststudy care of the subject's medical condition whether or not GSK is providing specific poststudy treatment.

6.11. Prior Medications and Nondrug Therapies

Prior medications will be reviewed and the investigator will attempt to obtain a complete history of any medications taken during the pregnancy (including the trimester of exposure, if possible) and during any previous episodes of preterm labor (e.g., magnesium sulfate or antenatal corticosteroid treatment).

6.12. Concomitant Medications and Nondrug Therapies

All concomitant medications taken by the mother during the study will be recorded in the eCRF; the indication for the concomitant medication must be specified. Prespecified concomitant medications of interest will be assessed. Concomitant medications taken during time of delivery and hospitalization will be obtained through a review of the hospital records.

6.12.1. Permitted Medications and Nondrug Therapies

6.12.1.1. Antenatal Corticosteroids

If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours. A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least 7 days prior to study enrollment.

6.12.1.2. Magnesium Sulfate

Investigators have the option to use magnesium sulfate. Magnesium sulfate should be given intravenously using a 4- to 6-g loading dose and 1- to 2-g/hour infusion rate. The total duration of magnesium sulfate administration should not exceed 48 hours. Doses exceeding this range will be considered a putative tocolytic and will be classified as a treatment failure.

6.12.1.3. Progesterone

Progesterone in any form and hydroxyprogesterone caproate may be continued for subjects already on established progesterone therapy for prevention of preterm birth but should not be initiated in subjects after they have been enrolled in the study. Established progesterone therapy refers to any formulation of progesterone supplementation intended for risk reduction of preterm birth.

6.12.1.4. Antibiotics

Intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection will be permitted.

6.12.1.5. Strong CYP3A4 Inhibitors

Drugs that are strong CYP3A4 inhibitors are permitted. Administration of strong CYP3A4 inhibitors concomitantly with IP requires an adjustment to the retosiban dosing regimen (see Section 6.3.2). A list of strong, moderate, and weak CYP3A4 inhibitors is provided in Appendix 7.

6.12.1.6. Strong CYP3A4 Inducers

Drugs that are strong CYP3A4 inducers are permitted. Administration of strong CYP3A4 inducers concomitantly with IP requires an adjustment to the retosiban dosing regimen (see Section 6.3.2). A list of strong, moderate, and weak CYP3A4 inducers is provided in Appendix 7.

6.12.1.7. Breast Cancer Resistance Protein or P-Glycoprotein Inhibitors

Drugs that are inhibitors of breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) are permitted during the study. A list of strong, moderate, and weak BCRP and P-gp inhibitors is provided in the SPM.

6.12.2. Prohibited Medications and Nondrug Therapies

Except for IP administered during this study, no additional investigational drugs or investigational devices are permitted for the mother from the time of study entry through completion of the follow-up visit (i.e., the maternal post-delivery assessment) or 30 days after administration of the last dose of IP, whichever is longer.

The use of a pessary may be continued for subjects who were using a pessary prior to the current episode of preterm labor; however, initiating use of a pessary during the study is prohibited.

6.12.2.1. Tocolytic Drugs

The concomitant medications listed below will be considered putative tocolytics when administered for active preterm labor or for the prevention of preterm labor. Apart from the exceptions listed in Table 4, use of any of the following putative tocolytics at any time prior to delivery will be considered a treatment failure:

- Calcium-channel blockers: nifedipine
- β-agonists: ritodrine, terbutaline, and salbutamol
- NSAIDs: celecoxib, ibuprofen, indomethacin, ketorolac, naproxen

Likewise, subjects administered any of the calcium-channel blockers, NSAIDs, or β-agonist medications listed above for maintenance tocolysis (prevention of recurrent preterm labor) who remained undelivered following the Inpatient Treatment Phase will be considered a treatment failure. Subjects administered doses of magnesium sulfate that exceed the dose specified in Section 6.12.1.2 (i.e., any dose that exceeds a 4- to 6-g IV loading dose and then a 1- to 2-g/hour infusion rate, with total duration of magnesium sulfate administration up to 48 hours) will also be considered a treatment failure.

Table 4 Guidelines for Exceptions to Putative Tocolytic Drug Use

Drug Class	Example Drugs	Exceptions for Use
Calcium-channel blockers	nifedipine	• Administration for chronic or pregnancy-induced hypertension will not be considered a treatment failure if the indication is provided when documenting concomitant medications. • Administration for new onset of hypertension would not be considered a treatment failure. The new onset must be recorded on the AE/SAE page of the eCRF. • A dose increase due to exacerbation of hypertension will be not considered a treatment failure. Exacerbation must be recorded on the AE/SAE page of the eCRF.
β-agonists	ritodrine, salbutamol, and terbutaline	• Administration for chronic or new onset respiratory indications is permitted. Acute short-term courses for respiratory conditions will not be considered a treatment failure if the indication is provided when documenting concomitant medications. • New onset of a respiratory condition would not be considered a treatment failure. The new onset must be recorded on the AE/SAE page of the eCRF. • A dose increase due to exacerbation of a respiratory condition will be not considered a treatment failure. Exacerbation to be recorded on the AE/SAE page of the eCRF.

Drug Class	Example Drugs	Exceptions for Use
NSAIDs[1]	celecoxib, ibuprofen, indomethacin, ketorolac, and naproxen	• Administration for chronic medical conditions, such as rheumatoid arthritis, will not be considered a treatment failure if the indication is provided when documenting concomitant medications. • Single doses of NSAIDs not taken for treatment of preterm labor (e.g., taken for headache, dysmenorrhea, or fever) will not be considered a putative tocolytic.

NSAID = nonsteroidal anti-inflammatory drug.

1. Subjects should be discouraged from using NSAIDs without first discussing with the investigator.

7. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Table 5).

As maternal subjects will be enrolled as part of an emergency situation, prestudy screening information that is collected by the study site may need to come from records that are obtained before the subject has signed the informed consent. Such information will only include items that are collected as part of standard care (e.g., symptoms of preterm labor, vital signs, cervical examination, medical and obstetrics history, and estimated GA). However, the subject will be required to provide informed consent for use of any information collected prior to consenting and before any additional study-specific procedures are performed.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

The following points must be noted:

- The timing and number of planned study assessments, including safety, PK, genetic, and biomarker assessments, may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File, which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form.

7.1. Time and Events Table

Table 5 Time and Events Table

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Post-Infusion Assessment Phase[1]		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	1-week face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery[2]	Delivery to 28 days post EDD	
Clinical and Other Assessments									
Written informed consent and medical releases for treatment[3]	X								
Discuss and request consent for participation in the infant follow-up study[4]		X◄	———	———	———	———	———	►X	X
Inclusion/exclusion criteria confirmation	X								
Baseline characteristics and demographic data	X								
Medical history (including obstetrics history)[5]	X								
Physical examination (including height and weight)	X								
Cervical examination[6]	X	X	X	X					
Estimated fetal weight and head circumference via ultrasound[7]	X								
Determine AFI via ultrasound[8]	X								
Uterine contractions[9]	X								

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase[1]**		**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**	**Withdrawal From Study**
	Day 0	**Day 1**	**Day 2**	**1-week face-to-face post-infusion visit**	**Weekly post-infusion telephone call**	**Information collected via medical records review**	**6 weeks after delivery[2]**	**Delivery to 28 days post EDD**	
Schedule post-infusion assessment visit			X						
Investigational Products[10]									
Retosiban or placebo		X	X						
Efficacy Assessments									
Date and time of delivery[11]						X			
Mode of delivery[11]						X			
Indication for delivery[11]						X			
Neonatal composite outcomes								X	
Neonatal hospital stay								X	
Maternal Safety Assessments									
Concomitant medications		X◄	———	———	———	———	►X		X
ECG 12-lead[12]	X								
Vital sign measurements (BP, pulse rate, temperature, respiratory rate, and oxygen saturation)[13]	X	X	X	X					
AEs, SAEs, and DREs : maternal		X◄	———	———	———	———	►X		X
Monitor fluid intake and output	X	X	X						
Breastfeeding status							X		
Edinburgh Postnatal Depression Scale[14](maternal)							X		

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase[1]**		**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**	**Withdrawal From Study**
	Day 0	**Day 1**	**Day 2**	**1-week face-to-face post-infusion visit**	**Weekly post-infusion telephone call**	**Information collected via medical records review**	**6 weeks after delivery[2]**	**Delivery to 28 days post EDD**	
Local laboratory assessments (LFTs only)[15]	X								
Central laboratory assessments (including hematology, chemistry, and LFTs)[16]	X		X	X[16]					
Physical examination (brief)				X					
Status of postpartum bleeding							X		
Fetal Safety Assessments									
Electronic fetal monitoring	X[17]	X[18]	X[18]	X[19]		X[20]			
AEs, SAEs, and DREs: fetal		X◄	———	———	———	►X			
Neonatal Safety Assessments									
AEs, SAEs, and DREs: neonatal						X◄	———	►X	
Neonatal Apgar Scores (1 and 5 minutes)[11]						X			
Neonatal growth parameters[11]						X			
Neonatal umbilical cord blood gases[11]						X			

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase[1]**		**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**	**Withdrawal From Study**
	Day 0	**Day 1**	**Day 2**	**1-week face-to-face post-infusion visit**	**Weekly post-infusion telephone call**	**Information collected via medical records review**	**6 weeks after delivery[2]**	**Delivery to 28 days post EDD**	
Health Outcome Assessments									
Maternal and neonatal health care resource use[21]						**X**		**X**	
Pharmacokinetic Assessments									
Maternal PK blood sample[22]		**X**[21] ◄——► **X**							
Cord blood sample[23]						**X**			
Breast milk/colostrum sample[24]						**X**			
Genetic and Biomarker Assessments									
Genetic blood sample for maternal DNA[25]	**X**								
Biomarker maternal blood sample[26]	**X**								
Genetic blood sample for cell-free fetal DNA[27]	**X**								
Other Assessments									
Fetal fibronectin (optional)[28]	**X**								
Cervical length via transvaginal ultrasound (optional)[29]	**X**								

AE = adverse event; AFI = amniotic fluid index; ALT = alanine aminotransferase; BP = blood pressure; DRE = disease-related event; ECG = electrocardiogram; eCRF = electronic case report form; EDD = estimated date of delivery; IP = investigational product; LFT = liver function test; PK = pharmacokinetic; SAE = serious adverse event; ULN = upper limit of normal.

1. Subjects who remain undelivered after 48 hours will return for a face-to-face post-infusion visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase. The subject will then be contacted every week via telephone to determine and record if she has delivered or experienced any subsequent

episodes of preterm labor. Note: If the subject is scheduled to visit the clinic for reasons not required by this protocol and/or she happens to be present at the time the telephone assessment is due, this assessment may be completed face-to-face.

2. During the Maternal Post Delivery Assessment Phase, subjects will be contacted by telephone within 6 weeks of delivery for a post-delivery assessment, including an assessment of AEs (±2 weeks), status of breastfeeding (±2 weeks), and completion of the EPDS (-2 weeks/+6 weeks).
3. Prestudy screening information that is collected by the study site may need to come from records that are obtained before the subject has signed the informed consent. The subject will be required to provide written informed consent before any study-specific procedures are performed, and the consent will request permission for use of any information collected prior to its having been signed.
4. During the study, the subject or other legal guardian for the infant (both delivered and undelivered) will be asked to give consent for the infant to participate in a separate long-term infant follow-up study for safety and neurodevelopment. Withdrawal from the study after beginning randomized treatment or discontinuing IP does not preclude involvement in the infant follow-up study.
5. Medical history will be collected at Screening. If a condition with a start date predating Day 0 (Screening) is subsequently discovered, the condition should be recorded in the Medical History eCRF. For obstetrics history, the investigator will make every effort to obtain this information either via computer records, directly from the subject's primary care obstetrician, or via telephone. However, in cases in which these records are not readily available (e.g., off hours, holiday), the investigator can use gestational age based on the verbal history from the subject with the intent of getting confirmation from the medical records or from the subject's primary care obstetrician as soon as possible.
6. A cervical examination (including dilation, effacement, and station) will occur at Screening, and an additional cervical examination may be performed before dosing based on investigator discretion. Additional cervical examinations (Day 1, Day 2, and/or at the 1-week face-to-face post-infusion assessment visit) are not required but may be performed based on investigator discretion. If inclusion criteria are based on cervical change (see Section 5.1), 2 examinations must be documented (either 2 digital cervical examinations or 2 cervical length examinations).
7. An ultrasound for estimation of fetal weight and head circumference is needed at Screening unless the date of the most recent ultrasound that includes fetal weight and head circumference is within 3 weeks (21 days) of the date of randomization.
8. The abdominal ultrasound for determination of the AFI will be performed at Screening for all subjects. The AFI should be measured using the 4-quadrant method.
9. Uterine tocography or manual palpation (if necessary) will be performed at Screening. Manual palpations will be permitted if there are technical challenges with measuring contraction frequency.
10. If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours. A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least 7 days prior to study enrollment. Investigators have discretion to use a standardized regimen of magnesium sulfate, as well as intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection.
11. Information regarding delivery will be obtained through a review of the hospital and medical records. Growth parameters include neonatal weight, length, and head circumference.
12. A 12-lead ECG will be performed prior to dosing. If the results are interpreted by the investigator to have clinically significant abnormalities, the subject cannot be dosed.
13. Blood pressure, pulse rate, respiratory rate, and temperature will be assessed at Screening, as part of maternal safety monitoring during the Inpatient Randomized Treatment Phase, and at the post-infusion assessment visit. During the Inpatient Randomized Treatment Phase, vital signs and oxygen saturation will be assessed and recorded within the following windows relative to the start of the infusion: 15 to 30 minutes, 4 to 8 hours, 20 to 24 hours, at the end of the infusion, at the time of any dose changes, and as warranted by a medical condition. Oxygen saturation less than 92% should be recorded as an AE or SAE, as appropriate.
14. Maternal subjects will complete the Edinburgh Postnatal Depression Scale, a self-reported questionnaire, at the maternal follow-up assessment 6 weeks (-2 weeks/+6 weeks) after delivery.

15. The LFTs should be ordered from the local laboratory before dosing with the IP. If the local laboratory results are available before the start of dosing, confirm that ALT is not ≥2 × ULN OR total bilirubin is not >1.5 × ULN (>35% direct bilirubin). An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%. With the exception of sites in Italy, screening LFT laboratory results do not need to be available for the subject to be randomly assigned to treatment or for the start of dosing with IP; however, see Section 5.3.3 if ALT or bilirubin is abnormal. **Sites in Italy**: Subjects must not be dosed before local laboratory LFT results are obtained and reviewed by the investigator, see Section 5.3.1.1 and Section 5.3.3 for details.
16. Hematology, chemistry, and LFTs will be determined through a central laboratory at the screening, Day 2, and the 1-week face-to-face post infusion assessment visits. The LFT values from the central laboratory should be reviewed for abnormalities (see Section 5.3.3). For subjects who deliver within 24 hours after completion or discontinuation of IP and for subjects who deliver at the investigative center after discharge but before the 1-week face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and LFTs should be performed. For subjects that do not deliver at the investigative center, central laboratory assessments for hematology, chemistry, and LFTs should be performed at the investigative center within 1 week (acceptable range: 3 to 14 days) after completion of the study drug infusion.
17. Prior to dosing, if the fetal heart rate pattern is nonreassuring, the subject cannot be dosed.
18. Electronic fetal monitoring is required for a minimum of 6 hours from the start of the infusion or from the start of a dose increase. As long as the fetal heart rate pattern is consistently reassuring throughout the required 6-hour duration of monitoring and the contraction frequency is ≤2 in a 30-minute window within the last hour of monitoring, continuous monitoring may be discontinued and nonstress tests initiated at a minimum of every 8 hours and as needed. Electronic fetal monitoring, including the fetal heart rate and fetal heart rate category, will be recorded in the eCRF with maternal vital signs. Any fetal heart rate assessment of Category II or III will be reported as an AE of special interest on a specified eCRF (details in Section 7.4.4).
19. If the subject has not delivered at the end of the Inpatient Randomized Treatment Phase, fetal heart rate will be recorded at the 1-week face-to-face post-infusion assessment visit. Any fetal heart rate assessment of Category II or III will be reported as an AE of special interest on a specified eCRF (details in Section 7.4.4).
20. During the Delivery Phase, fetal heart rate just prior to delivery will be collected, if available, from review of delivery records. Any fetal heart rate assessment of Category II or III will be reported as an AE of special interest on a specified eCRF (details in Section 7.4.4).
21. Maternal and neonatal health care resource use may include, but is not limited to, neonatal complications requiring intensive or specialized care, neonatal hospital readmission, and neonatal ambulatory surgery.
22. PK samples will be taken at each of the following sampling windows (relative to the start of the infusion on Day 1): 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 54 hours. In addition, a PK sample should be taken at the onset of any maternal or fetal SAE that occurs within 12 hours after completion or discontinuation of IP.
23. In subjects who deliver at an investigative center within 12 hours following completion or discontinuation of the IP, a single cord blood sample will be collected for PK analysis. Additionally, a maternal blood sample should be collected at the same time as the cord blood sample if the sample time does not already coincide with a PK sampling window (see Section 7.6.1).
24. A breast milk/colostrum sample is only to be collected in women who deliver and produce breast milk within 12 hours after completion or discontinuation of the IP.
25. All participating investigational centers will collect a blood sample for maternal DNA in women who provide informed consent for genetic research.
26. All participating investigational centers will collect a maternal blood sample for biomarker research.
27. Only US and Canadian investigational centers will collect a maternal blood sample for cell-free fetal DNA in women who provide informed consent for genetic research.
28. Fetal fibronectin results will be collected only at those institutions that perform fetal fibronectin testing as routine practice. Fetal fibronectin will not be used to determine study eligibility.
29. Cervical length determined by transvaginal ultrasound will be collected only at those institutions that measure cervical length as routine practice. Cervical length will not be used to determine study eligibility.

7.2. Screening and Critical Assessments Prior to Investigational Product Administration

The following assessments are required before dosing (i.e., before initiating randomized treatment):

- Electronic fetal monitoring to confirm that the fetal heart rate pattern remains reassuring
- Re-assess that tocolytic therapy is still indicated, according to the investigator's medical discretion.
- Liver function tests from a local laboratory to confirm that ALT is not ≥2 × ULN OR total bilirubin is not >1.5 × ULN (>35% direct bilirubin), if available. An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35% (see Section 5.3.3).With the exception of sites in Italy, dosing may be started prior to the availability of these results.

  Sites in Italy: Dosing must not be started prior to the availability of liver function tests results from a local laboratory (see Section 5.3.3).
- Electrocardiogram that is interpreted by the investigator to not have any significant abnormalities that may place the subject at risk for a cardiopulmonary complication during the study

If the fetal heart rate pattern is nonreassuring, tocolytic therapy is no longer indicated, levels of ALT or bilirubin are abnormal (if results are available), or the ECG has been interpreted to have clinically significant abnormalities, the subject cannot be dosed and will be withdrawn from the study (see Section 5.3.1).

7.3. Efficacy

7.3.1. Time to Delivery or Treatment Failure

The first of the two co-primary efficacy endpoints is a composite for the time elapsed between the beginning of treatment and delivery or treatment failure, whichever occurs first.

7.3.1.1. Time to Delivery

The time to delivery will be assessed from the start of study treatment administration (time 0) in the Inpatient Randomized Treatment Phase until delivery. For this efficacy assessment, medical records for the delivery and hospitalization for mother and newborn will be reviewed in order to record the following information:

- Date and time of delivery
- Mode of delivery
- Indication for delivery

Operational procedures will be instituted to optimize data collection and reporting consistency in those situations where the subject's delivery is performed by her referring primary care obstetrician. Details of these procedures are provided in the SPM.

7.3.1.2. Time to Treatment Failure

Treatment failure will be defined as the administration of any putative tocolytic medication for active preterm labor or as prevention of preterm labor, such as calcium-channel blockers, NSAIDs, or β-agonists, apart from the exceptions listed in Table 4, and magnesium sulfate doses that exceed a 4- to 6-g IV loading dose and 1- to 2-g/hour infusion rate and total duration of magnesium sulfate administration greater than 48 hours (see Section 6.12.1.2). The time to treatment failure will be assessed from the start of study treatment administration (time 0) in the Inpatient Randomized Treatment Phase until a putative tocolytic is administered.

Treatment failure will be considered to have occurred in the following situations:

- Administration of a putative tocolytic following IP discontinuation during the Inpatient Randomized Treatment Phase.
- Administration of a putative tocolytic in an undelivered subject for the management of recurrent preterm labor.
- Maintenance tocolysis is prohibited (Section 6.12.2.1); any subject treated with a tocolytic as maintenance treatment during the Post-infusion Assessment Phase will be considered a treatment failure.

For this efficacy assessment, the following information will be collected:

- Date and time of administration of any putative tocolytics
- Name and dose of the putative tocolytics
- Reason for administration of putative tocolytics

Operational procedures will be instituted to optimize data collection and reporting consistency in those situations when the subject is administered an alternative putative tocolytic by her referring primary care obstetrician. Details of these procedures are provided in the SPM.

7.3.2. Neonatal Composite and Other Outcomes

The proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite will be determined from time of delivery up to 28 days after the EDD of $40^{0/7}$ weeks. For infants who are still hospitalized 28 days post EDD, no further data will be collected as part of this study. Data after 28 days post EDD may be captured as part of a separate infant follow-up study.

For this efficacy assessment, newborn medical records will be reviewed in order to record the following information:

- Variables relevant to the composite (see complete list in Section 3, Primary Endpoints)
- Hospital length of stay
- Neonatal admission to a specialized care unit and length of stay
- Newborn hospital readmission and length of stay
- Ambulatory surgery

7.4. Safety

Planned time points for all safety assessments (maternal, fetal, and neonatal) are listed in the Time and Events Table (Table 5). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

During the Delivery Phase, the following safety information regarding the delivery and hospitalization for mother and newborn will be obtained through a review of the hospital records:

Maternal

- AEs and SAEs (Section 7.4.1)
- AEs of special interest (Section 7.4.1.4 and Appendix 4)
- Disease-related events (DREs) (Section 7.4.1.7.1)

Neonatal

- Apgar scores at 1 and 5 minutes
- Length, weight, and head circumference
- Umbilical cord blood gases (when available)
- AEs and SAEs (Section 7.4.1)
- AEs of special interest (Section 7.4.1.4 and Appendix 4)
- DREs (Section 7.4.1.7.2)

7.4.1. AEs and SAEs

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and their designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. Maternal, fetal, and neonatal AEs will be reported separately.

7.4.1.1. Time Period and Frequency for Collecting AE and SAE Information

- AEs and SAEs will be collected from the start of study treatment until the follow-up contact (see Section 7.4.1.3) at the time points specified in Table 5.
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF. Additionally, if a condition with a start date predating Day 0 (Screening) is subsequently discovered, the condition should be recorded in the Medical History eCRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK/PPD within 24 hours, as indicated in Appendix 3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK/PPD.

NOTE: The method of recording, evaluating, and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK/PPD are provided in Appendix 3

7.4.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 7.4.1.4) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.3.1.2). For newborns participating in the infant follow-up study, unresolved SAEs and AEs of special interest will be followed to stabilization or resolution in the long-term follow-up study. Further information on follow-up procedures is given in Appendix 3.

7.4.1.4. AEs of Special Interest

Certain AEs are of special interest for evaluating and characterizing the outcomes of women, fetuses, and/or neonates participating in this study. These AEs will be recorded on the events of special interest eCRFs pages in addition to the AE/SAE eCRF to capture additional details for the safety analyses.

Maternal, fetal, and neonatal AEs of special interest are listed in Section 3 and in Appendix 4. Guidelines for reporting these events are provided in Appendix 5.

7.4.1.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 (Section 12.3.3) and all deaths, whether or not they are considered SAEs, specific cardiovascular and death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at Screening. The cardiovascular eCRFs are presented as queries in response to reporting of certain cardiovascular Medical Dictionary for Regulatory Activities (MedDRA) terms. The cardiovascular information should be recorded in the specific cardiovascular section of the eCRF within 1 week of receipt of a cardiovascular event data query prompting its completion.

The death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

7.4.1.6. Congenital Anomalies

The proportion of infants with congenital anomalies diagnosed between the date of birth and 28 days post EDD will be assessed. NOTE: A congenital anomaly is a condition present at birth that results from malformation, deformation, or disruption in 1 or more parts of the body; a chromosomal abnormality; or a known clinical syndrome. Major congenital anomalies have a serious adverse effect on health, development, and functional ability or may require surgical or medical management. Minor anomalies are physical findings that vary from norms in the general population but do not cause increased morbidity.

When a congenital anomaly is reported, it will be reviewed by an expert in teratology who serves as the birth defect evaluator for this study. The birth defect evaluator's responsibilities will include the review, evaluation, and classification of all reports of birth defects. Additionally, he/she will provide an opinion regarding the possible etiologies for the development of the observed anomalies. The birth defect evaluator will reference medically confirmed reports in making the evaluation and issue targeted queries to the infant's heath care provider when necessary. If medical data are deemed insufficient to complete the evaluation, the birth defect evaluator may request additional medical evaluation of the infant.

For the purpose of this study, the US Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) criteria and the European Surveillance of Congenital Anomalies (EUROCAT) criteria will be used by the birth defect evaluator to code and classify congenital anomalies [EUROCAT, 2005; CDC, 2007].

Infants enrolled in the separate long-term infant follow-up study will be assessed for congenital anomalies diagnosed after 28 days post EDD.

7.4.1.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The DREs listed in Section 7.4.1.7.1 and Section 7.4.1.7.2 will be monitored by an internal GSK safety review team (reviewing blinded data).

7.4.1.7.1. Disease-Related Maternal Events

The following DREs are common maternal events during pregnancy, labor, and delivery:

- Signs and symptoms of labor discomfort (e.g., cramping, backache, muscle aches, nausea)
- Subsequent episodes of preterm labor (even if hospitalization is required) unless 1 of the conditions listed at the end of Section 7.4.1.7.2 applies
- Hospitalization for delivery, unless prolonged or 1 of the conditions listed at the end of Section 7.4.1.7.2 applies

7.4.1.7.2. Disease-Related Neonatal Events (Occurring in Infants Born Prior to 37 Completed Weeks)

The following DREs are common neonatal events related to prematurity and can be serious or life threatening:

- Lungs and respiratory system
  - Apnea (severe)
  - Respiratory failure due to fatigue, hypoxia, or air leak from alveolar injury
- Cardiovascular
  - Patent ductus arteriosus
  - Bradycardia
- Neurological
  - Ventriculomegaly
  - Cerebellar hemorrhage
  - Hydrocephalus other than congenital
- Gastrointestinal
  - Gastroesophageal reflux
  - Aspiration pneumonia
- Hematologic
  - Anemia
- Vision
  - Retinopathy of prematurity (all stages)
- Auditory
  - Hearing disorder
- Other
  - Temperature instability
  - Hypoglycemia

Because these events (Section 7.4.1.7.1 and Section 7.4.1.7.2) are typically associated with preterm labor and prematurity, they will not be reported according to the standard process for expedited reporting of SAEs to GSK/PPD (even though the event may meet the definition of a SAE). These events will be recorded on the DRE page in the eCRFs, and additional data will be recorded for any DREs related to study endpoints (see Section 3). These DREs will be monitored by the internal GSK safety review team.

However, if one or all of the following conditions apply, then the event should be reported as an AE/SAE as indicated in Appendix 3 (Section 12.3.4):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject,
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the IP, or
- An event defined as a disease-related neonatal event occurs in an infant born ≥37 completed weeks

7.4.1.8. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK/PPD of SAEs and nonserious AEs related to study treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK/PPD will comply with country specific-regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK/PPD will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.2. Physical Examinations

An admission physical examination will include at a minimum maternal height, weight, and assessment of heart, lungs, abdomen, and cervical examination including dilation, effacement, and station.

A brief physical examination, assessing heart, lungs, and abdomen, at a minimum, and, if undelivered, a cervical examination at the discretion of the investigator will be performed at the 1-week face-to-face post-infusion assessment visit, following conclusion of the treatment phase.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.4.3. Vital Signs and Oxygen Saturation

Blood pressure, pulse rate, respiratory rate, and temperature will be measured at the following time points during the study: Screening, Inpatient Randomized Treatment Phase, and at the 1-week face-to-face post-infusion assessment visit. During the Inpatient Randomized Treatment Phase, vital signs and oxygen saturation will be assessed and recorded within the following windows relative to the start of the infusion: 15 to 30 minutes, 4 to 8 hours, 20 to 24 hours, at the end of the infusion, at the time of any dose changes, and as warranted by a medical condition. Subjects may be either in a semirecumbent or seated position. Clinically relevant abnormal findings, including oxygen saturation less than 92%, should be recorded as an AE or SAE, as appropriate.

7.4.4. Electronic Fetal Monitoring

Electronic fetal monitoring is required for a minimum of 6 hours from the start of the infusion or from the start of a dose increase if the following are confirmed during monitoring:

- The fetal heart rate pattern is consistently reassuring throughout the required minimum 6-hour duration of monitoring
- The contraction frequency is ≤2 in a 30-minute window within the last hour of monitoring.

A reassuring nonstress test (defined as meeting Category I criterion), accounting for GA expectations, is required at a minimum of every 8 hours and as needed. An additional 6 hours of electronic fetal monitoring will be required for dose interruptions that are sufficiently long as to require an additional infusion of the IP.

Electronic fetal monitoring, including the fetal heart rate and fetal heart rate category, should be recorded in the eCRF at approximately the same time that maternal vital sign measurements are collected (Section 7.4.3). The electronic fetal heart rate tracing (paper or electronic) must be archived and retained in site records. Fetal heart rate will be recorded at the 1-week face-to-face post-infusion assessment visit if the subject remains undelivered. During the Delivery Phase, fetal heart rate just prior to delivery will be summarized, if available, from review of delivery records. Any fetal heart rate assessment of Category II or III according to the following criteria and based on ACOG guidelines [ACOG Practice Bulletin No. 106, 2009] will be reported as an AE of special interest on a specified eCRF in addition to the corresponding AE or SAE eCRF:

Category I fetal heart rate tracings include all of the following:

- Baseline rate: 110 to 160 beats per minute
- Baseline fetal heart rate variability: moderate
- Late or variable decelerations: absent
- Early decelerations: present or absent
- Accelerations: present or absent

Category II fetal heart rate tracings include all fetal heart rate tracings not categorized as Category I or III. Category II tracings may represent an appreciable fraction of those encountered in clinical care. Examples of Category II fetal heart rate tracings include any of the following:

- Baseline rate
  - Bradycardia not accompanied by absent baseline variability
  - Tachycardia
- Baseline fetal heart rate variability
  - Minimal baseline variability
  - Absent baseline variability with no recurrent decelerations
  - Marked baseline variability
- Accelerations
  - Absence of induced accelerations after fetal stimulation
- Periodic or episodic decelerations
  - Recurrent variable decelerations accompanied by minimal or moderate baseline variability
  - Prolonged deceleration more than 2 minutes but less than 10 minutes
  - Recurrent late decelerations with moderate baseline variability
  - Variable decelerations with other characteristics such as slow return to baseline, overshoots, or “shoulders”

Category III fetal heart rate tracings include either of the following:

- Absent baseline fetal heart rate variability and any of the following:
  - Recurrent late decelerations
  - Recurrent variable decelerations
  - Bradycardia
- Sinusoidal pattern

7.4.5. Abdominal Ultrasound

An abdominal ultrasound for determination of the AFI will be performed at Screening for confirmation that subject does not have evidence of polyhydramnios or oligohydramnios (per exclusion criterion 6, Section 5.2). The AFI should be measured using the 4-quadrant method (see SPM for details). An abdominal ultrasound to assess fetal growth will be done at Screening (unless records are available documenting an ultrasound-derived estimated fetal weight and head circumference within 3 weeks of Screening, with the results and date of assessment recorded in the eCRF).

7.4.6. Clinical Safety Laboratory Assessments

The following laboratory tests will be performed locally:

- Liver function tests, including ALT and bilirubin, performed at Screening (see Section 5.3.3)

If additional nonprotocol-specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), the results must be recorded in the eCRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood collections.

With the exception of the above, all protocol-required laboratory assessments must be performed by the central laboratory. For subjects that do not deliver at the investigative center, central laboratory assessments for hematology, chemistry, and LFTs should be performed at the investigative center within 1 week (acceptable range: 3 to 14 days) after completion of the study drug infusion.

Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and protocol Time and Events Table. Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

The volume of blood required for hematology, chemistry, and liver function tests, as specified in the Time and Events Table (Table 5), is approximately 20 mL.

7.4.7. Electrocardiogram

A single 12-lead ECG will be obtained prior to dosing (after the subject has been in a supine position for 10 to 15 minutes). If the investigator determines there is a clinically significant ECG abnormality, the subject will not be dosed and will be withdrawn from the study (Section 5.3.1.1). Performance of a follow-up ECG after an abnormal finding will be at the discretion of the investigator.

7.4.8. Fluid Management

Care should be taken to assess for fluid overload by monitoring the total fluid intake and output from the Screening Phase through Inpatient Randomized Treatment Phase and assessing for signs and symptoms of fluid overload. Details regarding this assessment are provided in the SPM.

7.4.9. Breastfeeding Status

At the maternal post-delivery assessment, the subjects will be asked questions regarding their breastfeeding status, as appropriate.

Details regarding this assessment are provided in the SPM.

7.4.10. Maternal Depression

The effect of preterm birth on maternal health status will be assessed using the EPDS. The EPDS is a 10-item self-reported assessment of depression, validated for administration during both the antenatal and the post-natal periods. Items are rated on a 4-point variable Likert scale, ranging from 0 to 3. A score of 12+ indicates an increased probability of depression and investigators or designated investigative center personnel will be notified immediately. Certain items in the scale also assess anxiety and will be used to assess level of anxiety. Maternal subjects will complete the EPDS at the maternal follow-up assessment 6 weeks (-2 weeks/+6 weeks) post-delivery (Table 5).

Additional details regarding the questionnaire administration, recording of health outcomes data, and collection and storage of the information are provided in the SPM.

7.5. Health Outcomes

- Assess maternal and neonatal health care resource use associated with preterm labor and preterm delivery. Health care resource use of interest includes:
    - Maternal and neonatal hospital admission (e.g., length of stay, hospital unit and type) and resource use (e.g., use of transport services, admission to extended stay facility)
    - Neonatal interventions of interest (e.g., parenteral nutrition, surfactants, blood products), procedures (e.g., imaging, such as ultrasound, computed tomography), and surgical procedures.

7.5.1. Health Outcomes – Maternal

7.5.1.1. Maternal Health Care Resource Use

Details on maternal health care resource use (both for hospitalizations related to preterm labor not resulting in a delivery and hospitalizations related to preterm labor/normal labor resulting in a delivery) associated with an episode of preterm labor, preterm delivery, and normal term delivery will be collected from review of medical records and recorded in the eCRF. The following information will be collected in the eCRF:

- Hospital admissions for preterm labor and normal term labor: number of hospital admissions related to preterm labor/preterm delivery, length of hospital stay (in days, hours) associated with hospital admission for preterm labor and normal term labor/term delivery, and associated hospital unit and type
- Health care resource use associated with preterm labor and normal term delivery: whether the mother was transported to the hospital and by what means (ground/aircraft), whether the mother was discharged to an extended stay facility for bed rest and days spent at extended stay facility prior to delivery, whether the mother was discharged home on uterine activity monitoring and days monitored, and delivery method (vaginal or caesarean section).

7.5.2. Health Outcomes – Neonatal

7.5.2.1. Neonatal Hospital Admission

For the delivery visit hospitalization, the length of the hospital stay (days) and associated hospital unit (neonatal intensive care unit, nursery level, or level of care 1 to 4) will be collected from review of medical records and recorded. In addition, whether the baby was transported to a different hospital or extended stay facility and length of stay (days) and number of hospital readmissions in the month following discharge from the delivery visit hospitalization will also be captured.

7.5.2.2. Neonatal Health Care Resource Use

Details of neonatal health care resource use associated with neonatal comorbidities of interest will be collected from review of medical records and recorded in the eCRF.

In addition to capturing health care resource use associated with neonatal morbidities, the following resource use, which may or may not be associated with neonatal comorbidities of interest, should be captured:

- Use of parenteral nutrition, including number of days of use
- Use of surfactant and number of doses administered
- Imaging (ultrasound, computed tomography, magnetic resonance imaging, radionuclide)
- Other surgical procedures

7.6. Pharmacokinetics

The PK analysis will determine retosiban clearance and volume of distribution and the effect of covariates on these parameters. Plasma analysis will be performed under the control of GSK PTS-Drug Metabolism and Pharmacokinetics (DMPK)/Scinovo. Concentrations of retosiban will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

7.6.1. Sampling

Maternal blood samples for the quantification of retosiban in plasma will be taken at the following sampling windows (relative to the start of the infusion on Day 1): 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 54 hours, the last point being after the end of the infusion. Samples may be taken at any time within these windows, but the exact time of the sample should be recorded in the eCRF. The volume of blood required for PK sampling, as specified in the Time and Events Table (Table 5), is approximately 8 mL.

Additionally, a maternal blood sample should be collected at the same time as the cord blood sample (see Section 7.6.2) if the sample time does not already coincide with one of the PK sampling windows listed above.

A blood sample also should be taken at the onset of any maternal or fetal SAE that occurs within 12 hours after completion or discontinuation of IP.

7.6.2. Umbilical Cord Blood

For those subjects who deliver at the investigative center within 12 hours following completion or discontinuation of IP, a single 3 mL cord blood sample will be collected for a PK analysis of fetal drug exposure. The date and time the sample was collected should be noted in the eCRF. If the investigator deems that umbilical cord blood is needed to provide care for the infant (e.g., neonatal transfusion or laboratory testing), collection for clinical use will be prioritized over PK sampling for the study.

7.6.3. Retosiban Levels in Breast Milk

If breast milk/colostrum is expressed within 12 hours of receiving study treatment, a small sample (0.25 mL) will be collected and analyzed to determine if retosiban is present in the sample. The date and time of the sample should be noted in the eCRF.

- Breast milk/colostrum produced prior to 4 hours of the completion or discontinuation of the study treatment will not be permitted to be consumed but will be collected for evaluation.

- A sample of breast milk/colostrum produced between 4 and 12 hours of the completion or discontinuation of the study treatment will be collected for evaluation, and the remainder can be consumed if the potential benefits to the infant are believed to outweigh the potential risks. The subject should be advised on the potential risks associated with feeding the infant her breast milk/colostrum that was expressed within 12 hours of the completion or discontinuation of the study treatment.
- Breast milk produced more than 12 hours after the completion or discontinuation of the study treatment will not be tested and there will be no restrictions on consumption given that the time frame is beyond 5 half-lives of retosiban.

7.7. Cervical Length

As routine practice, some institutions may measure cervical length by transvaginal ultrasound as an indicator of risk of delivery within hours to days. For these institutions already routinely performing this measurement, the cervical length data should be recorded in the eCRF. The data will not be used to determine eligibility but should be recorded for use in an exploratory analysis of cervical length as a marker of preterm labor and response to treatment. Additional details are provided in the SPM.

7.8. Fetal Fibronectin

Institutions that routinely perform fetal fibronectin (fFN) testing should record the result in the eCRF. Results will not be used to determine subject eligibility but will be used in an exploratory analysis of fFN as a marker of preterm labor and response to treatment. Details for sample collection and processing are in the SPM.

7.9. Biomarkers

A biomarker is a molecule associated specifically with a disease or condition such that it allows for the diagnosis, risk identification, or optimization of treatment. A 3.5-mL maternal blood sample for biomarker research will be collected at Screening. The samples will be stored and may be analyzed for future exploratory research.

7.10. Genetics

Pharmacogenetics is the study of how drug response varies in individuals due to genetic differences. Genetic differences also may contribute to preterm labor risk and progression. Two blood samples will be collected at Screening in subjects who provide informed consent for genetic research: a 6-mL sample for maternal DNA (at all participating investigational centers) and a 8.5-mL sample for cell-free fetal DNA (at US and Canadian investigational centers only).

Information regarding genetic research is included in Appendix 6.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK/PPD-defined eCRFs, transmitted electronically to GSK/PPD or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK/PPD standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- AEs, medical history, and surgical procedures will be coded using the current version of MedDRA, and concomitant medications terms will be coded using an internal validated medication dictionary, GSKDrug.
- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The co-primary endpoints assess prolongation of pregnancy using time to delivery or treatment failure, whichever comes first, and neonatal outcomes using a morbidity and mortality composite. The following are the null (H_0) and alternative (H_1) hypotheses for the co-primary endpoints in this study:

Time to delivery or treatment failure:

- H_0: prolongation of pregnancy as measured by time to delivery or treatment failure of women is equal between retosiban versus placebo
- H_1: prolongation of pregnancy as measured by time to delivery or treatment failure of women is unequal between retosiban versus placebo

Neonatal composite outcome:

- H_0: Incidence of neonatal composite outcome is equal between retosiban versus placebo
- H_1: Incidence of neonatal composite outcome is unequal between retosiban versus placebo

The hypotheses will be tested using a sequential testing procedure to control the overall type I error rate at the 5% level. Additionally, an O'Brian-Fleming alpha spending function will be employed to control the type I error for the planned interim analyses. The O'Brien-Fleming boundaries to be used at the second interim analysis and final analysis will be based on the actual information fraction, which will be the ratio of the actual sample size at the second interim analysis and the re-estimated final sample size (see Section 9.2.3). For example, if the actual sample size at the second interim analysis is 400 women/newborn pairs and the re-estimated sample size remains at

800 women/newborn pairs, the hypotheses would be tested at the 0.52% and 4.8% levels, respectively. Thus, at the second interim analysis, the hypothesis for time to delivery or treatment failure would be tested first at the 0.52% level, and the hypothesis for neonatal outcome would then be tested at the 0.52% level only if the null hypothesis for the time to delivery or treatment failure is rejected. Similarly, at the final analysis, the hypothesis for time to delivery or treatment failure would be tested first at the 4.8% level, and the hypothesis for neonatal outcome would then be tested at the 4.8% level only if the null hypothesis for the time to delivery or treatment failure is rejected. No further adjustments to the type I error rate are planned for the co-primary endpoints. Details of the methodologies to control the type I error will be included in the IDMC charter and study reporting and analysis plans (RAPs).

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

A total of 900 women (450 women in each group) will be recruited into the study and randomly assigned to ensure that 800 (400 women/newborns in each group) have recorded birth data, which provides 86% statistical power to detect a relative risk of 68% between retosiban and placebo in neonatal outcomes in the proposed adaptive design with futility stopping, success stopping, and sample size re-estimation. Calculations assume a placebo incidence rate of 34%.

Additionally, the sample size of 800 women (400 women/newborn pairs per group) provides at least 90% statistical power to detect a difference of 5.5 days in the co-primary endpoint, time to delivery or treatment failure, and the key secondary endpoint, time to delivery, between retosiban and placebo.

The sample size calculations are based on a 2-sided testing procedure with a type I error rate of 4.8% (e.g., O'Brien-Fleming boundary based on planned information fraction) and an approximate 10% dropout rate. Calculations are based on simulations and assume that the percentage of women enrolled into each of the GA strata $24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$, and $31^{0/7}$ to $33^{6/7}$ will be 7%, 13%, 27%, and 53% (1:2:4:8 ratio), respectively, and approximately 55% of women in the placebo arm will deliver within the 3 weeks of randomization. The details of model assumption and simulation are on file with GSK.

9.2.2. Sample Size Sensitivity

It is expected that the placebo incidence rate of the co-primary endpoint of neonatal morbidity and mortality composite will be dependent on the percentage of women enrolled into each of the GA strata, the percentage of women that deliver within 3 weeks of randomization, and the frequency of neonatal composite. Subsequently, the power of the study to detect a relative risk of 68% between retosiban and placebo in neonatal outcomes is expected to be sensitive to the assumptions used to determine the study sample size.

Further work has been done by GSK (details on file with GSK) to evaluate the sensitivity of the power of the study to detect a relative risk reduction in neonatal outcomes if the

assumptions do not hold. In those analyses, the power of the study was most sensitive to assumptions regarding the percentage of women that delivered within 3 weeks of randomization and the frequency of neonatal composite. If these are modestly lower than expected, such that the placebo response rate is 28%, then the power of the study will be approximately 76% to detect a relative risk of 68% between retosiban and placebo in neonatal outcomes. If these are significantly lower, such that the placebo response rate is 22%, the power of the study could be as low as 60%.

In order to mitigate the uncertainty around these assumptions, the proposed adaptive design allows for the sample size of the study to be increased following the second interim analysis (see Section 9.3.4).

9.2.3. Sample Size Re-Estimation or Adjustment

The sample size may be adjusted at the second interim analysis. The sample size re-estimation will be conducted in a manner to maintain the study blind and will be carried out prior to the formal statistical interim analysis described in Section 9.3.4 The re-estimation sample size will be based only on the blinded observed overall pooled rate of neonatal composite and will be conducted by the blinded team. The sample size may be increased by a minimum of 50 women/newborn pairs up to a maximum sample size of 1200 women/newborn pairs. The re-estimated sample size in conjunction with the actual sample size for the second interim analysis will be used to determine the O'Brien-Fleming boundaries to be used in the interim and final analyses.

The details of the sample size re-estimation methods and determination of the corresponding O'Brien-Fleming boundaries will be provided in the RAP.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations (Maternal)

9.3.1.1. Maternal Safety Population

The Maternal Safety Population is defined as all subjects randomly assigned to treatment that have been exposed to study treatment. Randomly assigned subjects will only be excluded if there is clear evidence the subject did not receive IP. Subjects will be analyzed according to their actual treatment in case this differs from their randomized treatment. This will be the primary population for assessing maternal and fetal safety.

9.3.1.2. Maternal ITT Population

The Maternal ITT Population, also known as the full analysis set, comprises all randomly assigned subjects who have been exposed to study treatment. Subjects who are randomly assigned but fail to receive any study treatment (as described in Section 5.3.1.1) will be excluded from the ITT Population. This is the primary analysis data set and will be used for evaluation of all maternal and fetal efficacy endpoints.

9.3.1.3. Maternal Per-Protocol Population

This Maternal Per-Protocol Population is defined as all subjects in the Maternal ITT Population excluding those who are major protocol violators. Subjects will be analyzed according to their actual treatment in case this differs from their randomly assigned treatment. This will include exclusions for use of prohibited concomitant medications and treatment failure to meet inclusion criteria specified by the protocol.

9.3.2. Analysis Population (Neonatal)

9.3.2.1. Neonatal Safety Population

The Neonatal Safety Population is defined as neonates whose mothers received randomized treatment. The neonates will be analyzed according to the actual treatment the mother received in case this differs from randomized treatment. This will be the primary population for assessing neonatal safety.

9.3.2.2. Neonatal ITT Population

The Neonatal ITT Population, also known as the full analysis set, comprises all neonates of mothers who were randomly assigned subjects exposed to study treatment. This population is the primary analysis data set and will be used for evaluation of all neonatal efficacy endpoints.

9.3.2.3. Neonatal Per-Protocol Population

The Neonatal Per-Protocol Population is defined as all subjects in the Neonatal ITT Population excluding those with major protocol violations.

9.3.3. Treatment Comparisons

9.3.3.1. Primary Comparisons of Interest

The primary comparison of interest is retosiban versus placebo for the co-primary endpoints: time to delivery or treatment failure and neonatal composite endpoint. The comparison will be based on the ITT Population, and a sequential testing procedure will be used to control the overall type I error rate at 5% level with time to delivery or treatment failure being tested first.

9.3.3.2. Other Comparisons of Interest

The comparison of retosiban versus placebo will also be performed for key secondary endpoints: time to delivery, proportion of preterm births (<$37^{0/7}$ weeks' gestation), proportion of births ≥$37^{0/7}$ weeks' gestation, and neonatal length of hospital stay. Other comparisons of exploratory endpoints between retosiban and placebo will be discussed in the RAP.

9.3.3.3. Subgroup Analysis

Additionally, comparisons of retosiban versus placebo for co-primary and key secondary endpoints may also be performed for the following subgroups:

- GA strata $24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$, or $31^{0/7}$ to $33^{6/7}$
- Established progesterone use (yes or no)
- Magnesium sulfate use
- Putative tocolytic use following IP discontinuation

Other potential subgroup comparisons will be described in the RAP.

9.3.3.4. Exploratory Covariate Analyses

Other exploratory covariate analyses will be performed to examine the relationship between the treatment response and potential covariates including baseline fFN value, subclinical intrauterine infection, and other concomitant medications. Details of analysis will be included in final RAP.

9.3.4. Interim Analyses

Two interim analyses are planned. The first interim analysis will occur after approximately 150 subjects have completed delivery and have time-to-delivery results available. The primary objective of the first interim analysis is to determine if the study should be terminated for lack of efficacy (futility) based on prespecified criteria. The decision will be based primarily on the analysis of the key secondary endpoint of time to delivery; however, all available safety and efficacy data will be reviewed.

Time to delivery will be analyzed similarly to analyses described in Section 9.4.1.1. An estimate of the difference in time to delivery between the retosiban and placebo groups will be computed. Additionally, the conditional power of rejecting the null hypothesis at the end of the study based on the observed difference will be computed.

The second interim analysis will occur after approximately 400 women/newborn pairs are followed up to 28 days post EDD. The primary objectives of the second interim analysis are to determine if the study should be terminated for either lack of efficacy (futility) or for greater than expected efficacy (success). The decision to terminate for futility will be based on prespecified criteria, the key secondary endpoint of time to delivery, and the co-primary endpoint of neonatal composite. The decision to stop for success will be based on the sequential testing of the null hypotheses for co-primary endpoints (time to

delivery or treatment failure and then neonatal composite) at the determined O'Brian-Fleming boundary (the adjusted alpha level based on an O'Brian-Fleming alpha spending function and the actual sample size at the second interim analysis and re-estimated sample size at the end of the study, see Section 9.2.3). Decisions will be based on prespecified criteria, although all available safety and efficacy data will be reviewed.

Time to delivery or treatment failure and the neonatal composite will be analyzed as described in Section 9.4.1.1. Point estimate and associated p-value for both the difference in time to delivery or treatment failure and the odds ratio of a neonatal composite occurring between retosiban and placebo will be computed. Additionally, the conditional power of rejecting the null hypothesis at the end of the study based on the observed odds ratio of the neonatal composite will be computed.

9.4. Key Elements of Analysis Plan

9.4.1. Efficacy Analyses

9.4.1.1. Primary Analyses

The primary objective of the statistical analysis will be to test the null hypothesis in the ITT Population that there is no difference between retosiban and placebo versus the alternative hypothesis that there is a difference between the 2 co-primary endpoints. The hypotheses tests will be assessed and confidence intervals constructed using the adjusted alpha level determined by the O'Brien-Fleming boundaries.

The primary analysis of time to delivery or treatment failure will utilize a finite mixture model [McLachlan, 2000] with 2 components, 1 for those women delivering imminently and the other for the women delivering at term. The exact weight of each component will be determined by the observations from these component and model concomitant variables, including treatment, established progesterone use, and GA at randomization. Within each component, the expected time to delivery or treatment failure will be modeled as a function of treatment as fixed effect and GA at randomization and established progesterone use (yes or no) as covariates. The model parameters will be estimated using expectation maximization algorithm. Point estimates, associated 100(1-α)% confidence intervals (CIs), and p-values for the overall average difference in time to delivery or treatment failure between retosiban and placebo will then be derived using a weighted average of model parameter estimates and variance from each subpopulation of the mixture model.

For the neonatal composite outcome endpoint, a logistic regression model will be used for comparing retosiban with placebo, with progesterone use (yes or no) and GA at randomization as covariates. The model will use a logit link function to estimate the log odds of percentage of preterm birth. The model will include terms for treatment group, established progesterone use, and GA at randomization. The number and percentage of subjects in each treatment group, the odds ratio of response rates (retosiban versus placebo), 100(1–α)% CIs for the odds ratio of response rates, and p-value will be presented. The relative risk response rates will be computed from the odds ratio.

9.4.1.2. Secondary Analyses

9.4.1.2.1. Key Secondary Analyses

The key secondary analysis for this study includes time to delivery, the proportion of births prior to $37^{0/7}$ weeks' gestation, proportion of births at term ($37^{0/7}$ to $41^{6/7}$ weeks' gestation), and length of neonatal hospital stay. To preserve the overall type I error rate, the key secondary analysis will be performed if and only if the null hypothesis of the primary endpoint is rejected. In addition, a stepwise Holm's test will be used to adjust for multiplicity of the key secondary endpoints such that the type I error rate will be maintained at 5%. The endpoint of time to delivery will be analyzed as described in Section 9.4.1.1.

The endpoints of proportion of births prior to $37^{0/7}$ weeks' gestation and proportion of births at term ($37^{0/7}$ to $41^{6/7}$ weeks' gestation) will be analyzed analogous to the co-primary neonatal composite outcome endpoint.

Length of hospital stay will be log-transformed prior to analysis. Log-transformed length of hospital stay will be analyzed using an analysis of covariance adjusting for the covariate of established progesterone use (yes or no) and GA at randomization. Other covariates may be added at discretion of the study statistician. The model-adjusted length of stay will be presented for each treatment group. In addition, the treatment difference between retosiban and placebo and associated CIs and p-values will be presented.

The Wilcoxon rank sum test will also be performed for length of hospital stay if the assumption of normality is violated after log transformation.

Additionally, interactions between GA at randomization and treatment and established progesterone use and treatment will also be investigated.

9.4.1.2.2. Other Secondary and Exploratory Analysis

Binary secondary analysis endpoints will be analyzed in a similar fashion to the neonatal composite analysis. Binary exploratory endpoints will be analyzed in a similar fashion to the key secondary endpoints. The details of analysis will be provided in the RAP.

9.4.2. Safety Analyses

No formal hypothesis statistical test will be performed for the safety data. All safety analyses will be performed using the Safety Population, unless otherwise specified. The objective of the safety analysis is to describe the maternal, fetal, and neonatal safety profile during/after IV retosiban treatment as compared with placebo treatment. As such, maternal, fetal, and neonatal safety data will be summarized by treatment group.

All summary statistics of continuous variables will include the following: number of subjects, mean, median, standard deviation, minimum, and maximum. For binary outcomes, all summary tables will include the number and percentage of subjects with the response/event. All summary tables will include N for each group (i.e., the total number of subjects randomly assigned to each group within the appropriate population).

To further describe the maternal, fetal, and neonatal safety profile of retosiban, a GA of pregnancy at randomization subgroup may be explored.

For this subgroup, maternal, fetal, and neonate safety data will be summarized by treatment and subgroup, as described above. Other potential subgroup comparisons will be described in the RAP.

9.4.2.1. Extent of Exposure (Maternal)

The total volume administered during the infusion and the total study drug administered will be listed and summarized. If applicable, the number of infusion interruptions and the time taken for each infusion will be summarized. The frequency and percentage of women who discontinued study treatment and who had a dose increase will be presented. Full details of the extent of exposure will be provided in the RAP.

9.4.2.2. Adverse Events

Adverse events will be coded using the MedDRA dictionary and grouped by body system. Adverse events will be summarized by treatment group. Within each group, AEs will be summarized by frequency and proportion of total subjects, by event type, and by category of body system. Separate summaries will be given for all AEs, drug-related AEs, SAEs, and AEs leading to discontinuation. Where appropriate, the AEs will be summarized by maternal, fetal, and neonatal events separately.

The proportion of subjects reporting at least 1 AE, 1 IP-related AE, 1 SAE, and 1 AE leading to discontinuation will also be calculated for each group.

Adverse events of special interest (see Section 7.4.1.4 and Appendix 4) and DREs (see Section 7.4.1.7) will be similarly summarized.

Full details of all safety analyses including AEs, SAE, AEs of special interest, DREs, clinical laboratory evaluations, and vital sign measurements will be provided in the RAP.

9.4.3. Health Outcomes Analyses

Analysis of neonatal length of stay, one of the key secondary endpoints, is described in Section 9.4.1.2.1. All other health outcomes will be analyzed using the ITT Population, unless otherwise specified. The objective of the analysis is to compare the health outcomes profile in mother/infant receiving IV retosiban treatment as compared with placebo treatment. The details of this analysis will be included in the final RAP.

In addition, all healthy outcomes will be summarized by treatment group. The summary statistics of continuous variables will include the following: number of subjects, mean, median, standard deviation, minimum, and maximum. For binary outcomes, all summary tables will include the number and percentage of subjects with the response/event. All summary tables will include N for each group (i.e., the total number of subjects randomly assigned to each group within the appropriate population).

To further describe the health outcomes of retosiban, the following subgroups may be explored:

- GA of pregnancy at randomization
- Established progesterone use
- Magnesium sulfate use
- Putative tocolytic use following IP discontinuation
- Region/sites

9.4.4. Pharmacokinetic Analyses

The PK data will be analyzed using a nonlinear mixed-effects approach. The details of the analysis will be provided in a separate RAP.

9.4.5. Genetic Analyses

Any genetic analyses may be reported concurrently with the clinical study report or described in a separate genetic research analysis plan and may be reported separately from the main clinical study report. See Appendix 6 for details about the genetic research analysis plan.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments, as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g., reporting of AEs/SAEs/protocol deviations to IRB/IEC)

GSK/PPD will provide full details of the above procedures, either verbally, in writing, or both.

- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations, including GCP and GSK/PPD procedures, PPD monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK/PPD requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify that the

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements

The investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK/PPD may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues, and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the PPD monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, including GCP and GSK/PPD standard operating procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

- If the study is suspended or prematurely discontinued for safety reasons, GSK/PPD will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institution(s) conducting the study. GSK/PPD will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK/PPD audit or regulatory inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK/PPD will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK/PPD standards/procedures, and/or institutional requirements.
- The investigator must notify GSK/PPD of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK policy.

10.8. Independent Data Monitoring Committee

This study will be conducted under the auspices of an IDMC. The membership and activities are outlined in the IDMC charter. This committee will review the accumulating data as the study progresses, as well as data across the retosiban program.

11. REFERENCES

American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Practice Bulletin No. 76. Postpartum hemorrhage. Obstet Gynecol. 2006;108(4):1039-47.

American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Practice Bulletin No. 106. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol. 2009;114(1):192-202.

American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Practice Bulletin No. 127. Management of preterm labor. Obstet Gynecol. 2012;119(6):1308-17.

Bain ES, Middleton PF, Crowther CA. Maternal adverse effects of different antenatal magnesium sulphate regimens for improving maternal and infant outcomes: a systematic review. BMC Pregnancy Childbirth. 2013;13:195.

Benedetto MT, DeCicco F, Rossiello F, Nicosia AL, Lupi G, Dell'Acqua S. Oxytocin receptor in human fetal membranes at term and during labor. J Steroid Biochem. 1990;35:205-8.

Berkowitz GS, Blackmore-Prince C, Lapinski RH, Savitz DA. Risk factors for preterm birth subtypes. Epidemiology. 1998;9(3):279-85.

Centers for Disease Control and Prevention (CDC). Metropolitan Atlanta Congenital Defects Program (MACDP) birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies. August 2007. Available from: http://www.cdc.gov/ncbddd/birthdefects/documents/macdpcode0807.pdf. (Accessed 05 Nov 2014).

Conde-Agudelo A, Romero R. Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: a systematic review and metaanalysis. Am J Obstet Gynecol. 2009;200(6):595-609.

Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Database Syst Rev. 2009;(1):CD004661.

Endler M, Grünewal C, Saltvedt S. Epidemiology of retained placenta: oxytocin as an independent risk factor. Obstet Gynecol. 2012;119(4):801-9.

European Surveillance of Congenital Anomalies (EUROCAT). Guide 1.3: Instructions for registration of congenital anomalies. Belfast: EUROCAT Central Registry, University of Ulster, 2005. Available from: http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf. (Accessed 05 Nov 2014).

Fuchs AR, Fuchs F, Husslein P, Soloff MS, Fernstrom MJ. Oxytocin receptors and human parturition: a dual role for oxytocin in the initiation of labor. Science. 1982;215(4538):1396–8.

GlaxoSmithKline Document Number CM2006/00201/05. Investigator's brochure GSK716755. 29-Jun-2016.

Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.

Goldenberg RL, Iams JD, Mercer BM, et al. The preterm prediction study: the value of new vs standard risk factors in predicting early and all spontaneous preterm births. NICHD MFMU Network. Am J Public Health. 1998;88(22):233-8.

Goldenberg RL. The management of preterm labor. Obstet Gynecol. 2002;100(5 Pt 1):1020-37.

Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A. Tocolytics for preterm labor: a systematic review. Obstet Gynecol. 1999;94(5 Pt 2):869-77.

Lockwood CJ, Kuczynski E. Risk stratification and pathological mechanisms in preterm delivery. Paediatr Perinat Epidemiol. 2001;15 Suppl 2:78-89.

Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Wilson EC, Mathews TJ. Births: final data for 2010. Natl Vital Stat Rep. 2012;61(1):1-72.

Mathews TJ, MacDorman MF. Infant mortality statistics from the 2006 period linked birth/infant death data set. Natl Vital Stat Rep. 2010;58(17):1-31.

McLachlan G, Peel D. Finite mixture models. New York (NY): John Wiley & Sons, Inc; 2000.

Meis PJ, Goldenberg RL, Mercer BM, et al. The preterm prediction study: risk factors for indicated preterm births. Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development. Am J Obstet Gynecol. 1998;178(3):562-7.

Pennell CE, Jacobsson B, Williams SM, et al. Genetic epidemiologic studies of preterm birth: guidelines for research. Am J Obstet Gynecol. 2007;196(2):107-18.

Romero R, Mazor M, Munoz H, Gomez R, Galasso M, Sherer DM. The preterm labor syndrome. Ann N Y Acad Sci. 1994;734:414-29.

Roos C, Spaanderman ME, Schuit E, et al; APOSTELL-II Study Group. Effect of maintenance tocolysis with nifedipine in threatened preterm labor on perinatal outcomes: a randomized controlled trial. JAMA. 2013;309(1):41-7.

Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline No. 7. Antenatal corticosteroids to reduce neonatal morbidity. Royal College of Obstetricians and Gynaecologists. October 2010. Available from:

https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-7.pdf (Accessed 05 Nov 2014).

Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline No. 1B. Tocolytic for women in preterm labour. February 2011a. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg1b/ (Accessed 05 Nov 2014).

Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371(9608):261-9.

Samol JM, Lambers DS. Magnesium sulfate tocolysis and pulmonary edema: the drug or the vehicle? Am J Obstet Gynecol. 2005;192(5):1430-2.

Sanchez-Ramos L, Kaunitz AM, Gaudier FL, Delke I. Efficacy of maintenance therapy after acute tocolysis: a meta-analysis. Am J Obstet Gynecol. 1999;181(2):484-90.

Simhan HN, Caritis SN. Prevention of preterm delivery. N Engl J Med. 2007;357(5):477-87.

Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010;126(3);443-56.

Stones RW, Paterson CM, Saunders NJ. Risk factors for major obstetric haemorrhage. Eur J Obstet Gynecol Reprod Biol. 1993;48(1):15-8.

Thornton S, Goodwin TM, Greisen G, Hedegaard M, Arce JC. The effect of barusiban, a selective oxytocin antagonist, in threatened preterm labor at late gestational age: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol. 2009;200(6):627e1-627e10.

Tucker JM, Goldenberg RL, Davis RO, Copper RL, Winkler CL, Hauth JC. Etiologies of preterm birth in an indigent population: is prevention a logical expectation? Obstet Gynecol. 1991;77(3):343-7.

Valenzuela GJ, Craig J, Bernhardt MD, Holland ML. Placental passage of the oxytocin antagonist atosiban. Am J Obstet Gynecol.l 1995;172(4 Pt 1):1304-6.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AE	adverse event
AFI	amniotic fluid index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
CDC	Centers for Disease Control and Prevention
CI	confidence interval
cm	centimeter
CYP3A4	cytochrome P450 3A4 enzyme
DMPK	Drug Metabolism and Pharmacokinetics
DRE	disease-related event
ECG	electrocardiogram
eCRF	electronic case report form
EDD	estimated date of delivery
EPDS	Edinburgh Postnatal Depression Scale
EUROCAT	European Surveillance of Congenital Anomalies
fFN	fetal fibronectin
GA	gestational age
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
IB	investigator's brochure
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IVH	intraventricular hemorrhage
IVRS	interactive voice response system
IWRS	interactive web response system
kg	kilogram
L	liter
MACDP	Metropolitan Atlanta Congenital Defects Program
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
msec	millisecond

NaCl	sodium chloride
ng	nanogram
NSAID	nonsteroidal anti-inflammatory drug
pg	picogram
P-gp	P-glycoprotein
PK	pharmacokinetic
PPROM	preterm premature rupture of membranes
QTc	corrected QT interval
QTcF	corrected QT interval using the Fridericia formula
RAP	reporting and analysis plan
RCOG	Royal College of Obstetricians and Gynecologists
RDS	respiratory distress syndrome
SAE	serious adverse event
SPM	Study Procedures Manual
ULN	upper limit of normal

Definitions

Chronological age	Defined as the time elapsed after birth; it is usually described in days, months, and years
Estimated date of delivery	Defined as $40^{0/7}$ weeks' gestation for all subjects
Gestational age	Determined by (1) known fertilization date, either *in vitro* fertilization or intrauterine insemination or (2) a best estimated due date confirmed or established by the earliest ultrasound performed before $24^{0/7}$ weeks gestation.
Postmenstrual age	Determined by adding chronological age to gestational age at delivery

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA

12.2. Appendix 2: Liver Safety Required Actions and Follow-up Assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-Absolute	ALT ≥8 × ULN
ALT-Increase	ALT ≥5 × ULN but <8 × ULN persists for ≥2 weeks ALT ≥3 × ULN but <5 × ULN persists for ≥4 weeks
Bilirubin[1,2]	ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin)
INR[2]	ALT ≥3 × ULN and INR >1.5, if INR measured
Cannot Monitor	ALT ≥5 × ULN but <8 × ULN and cannot be monitored weekly for ≥2 weeks ALT ≥3 × ULN but <5 × ULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow-up Assessments Following ANY Liver Stopping Event	
Actions	**Follow-up Assessments**
• Immediately discontinue study treatment • Report the event to GSK/PPD **within 24 hours** • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment but continue subject in the study for any protocol-specified follow-up assessments	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5] • A blood sample for pharmacokinetic analysis will be obtained within 12 hours of last dose (completion or discontinuation)[6] • Serum creatine phosphokinase and lactate dehydrogenase • Fractionated bilirubin, if total bilirubin ≥2 × ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form

MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, ALP, bilirubin) and perform liver event follow-up assessments within **24 hours** • Monitor subjects twice weekly until liver chemistries resolve, stabilize, or return to within baseline • A specialist or hepatology consultation is recommended **<u>For all other criteria:</u>** • Repeat liver chemistries (include ALT, AST, ALP, bilirubin) and perform liver event follow-up assessments within **24 to 72 hours** • Monitor subjects weekly until liver chemistries resolve, stabilize, or return to within baseline	including acetaminophen, herbal remedies, other over-the-counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Antinuclear antibody, antismooth muscle antibody, type 1 antiliver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computed tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IgM = immunoglobulin M; INR = international normalized ratio; eCRF = electronic case report form; GSK = GlaxoSmithKline; HPLC = high-performance liquid chromatography; PK = pharmacokinetic; SAE = serious adverse event; ULN = upper limit of normal.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥3 × ULN **and** bilirubin ≥2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 x ULN **and** INR >1.5, if INR measured, which may indicate severe liver injury (possible "Hy's Law"), **must be reported as an SAE** (**excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash, or eosinophilia).
4. Includes: hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen, and hepatitis B core antibody (IgM); hepatitis complementary RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); hepatitis E IgM antibody.
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. The PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample collection and the date/time of the last dose of study treatment prior to blood sample collection on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

Liver Chemistry Increased Monitoring Criteria With Continued Therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5 × ULN and <8 × ULN **and** bilirubin <2 × ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3 × ULN and <5 × ULN **and** bilirubin <2 × ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the PPD medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize, or return to within Baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5 × ULN and <8 × ULN to ≥3 × ULN but <5 × ULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3 × ULN and bilirubin <2 × ULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GSK = GlaxoSmithKline; ULN = upper limit of normal.

References

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009;37(8):1779-84.

Le Gal F, Gordien E, Affolabi D, et al. Quantification of hepatitis delta virus RNA in serum by consensus real-time PCR indicates different patterns of virological response to interferon therapy in chronically infected patients. J Clin Microbiol. 2005;43(5):2363-9.

12.3. Appendix 3: Definition of and Procedures for Recording, Evaluating, Following Up, and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/serious AE (SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.) • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening NOTE: The term "life threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Is associated with liver injury and impaired liver function defined as:

- Alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) and total bilirubin* ≥2 × ULN (>35% direct)

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3 × ULN and total bilirubin ≥2 × ULN, then the event is still to be reported as an SAE.

12.3.3. Definition of Cardiovascular Events

Cardiovascular event definition:
Investigators will be required to fill out the specific cardiovascular event page of the electronic case report form (eCRF) for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.3.4. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GlaxoSmithKline (GSK)/PPD AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by GSK/PPD. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK/PPD. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.3.5. Evaluating AEs and SAEs

Assessment of intensity:
The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to an intensity category. Refer to the SPM for details on assessing intensity of maternal and fetal AEs and SAEs. • Note: An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE.

Assessment of causality:
• The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. • A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. • The investigator will also consult the investigator brochure and/or product information, for marketed products, in the determination of his/her assessment. • For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK/PPD. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK/PPD.** • The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs:
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK/PPD to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK/PPD with a copy of any postmortem findings, including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE or AE of special interest data to GSK/PPD within the designated reporting time frames.

12.3.6. Reporting of SAEs to GSK/PPD

SAE reporting to GSK/PPD via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK/PPD will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE hotline fax number, as provided on medical monitor/sponsor information page of the protocol. • Site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the “reviewed” box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or by telephone using the SAE hotline telephone number, as provided on medical monitor/sponsor information page of the protocol. • Contacts for SAE receipt can be found at the beginning of this protocol on the sponsor/medical monitor contact information page.

12.4. Appendix 4: Adverse Events of Special Interest

The safety endpoints in this study include the following maternal, fetal, and neonatal adverse events (AEs) of special interest:

Maternal AEs of special interest

- Maternal death
- Chorioamnionitis and its complications
    - Clinical chorioamnionitis, preterm premature rupture of membranes, endomyometritis, wound infection, pelvic abscess, bacteremia, septic shock, disseminated intravascular coagulation, and adult respiratory distress syndrome (RDS)
- Placental abruption
- Postpartum hemorrhage – postpartum hemorrhage and/or retained placenta
- Pulmonary edema

Fetal AEs of special interest:

- Intrauterine fetal demise
- Category II or III fetal heart rate tracing (defined according to American College of Obstetricians and Gynecologists [ACOG] Practice Bulletin 106 [ACOG Practice Bulletin No. 106, 2009])
- Fetal inflammatory response syndrome characterized by cord blood interleukin-6 >11 pg/mL, funisitis, or chorionic vasculitis

Neonatal AEs of special interest:

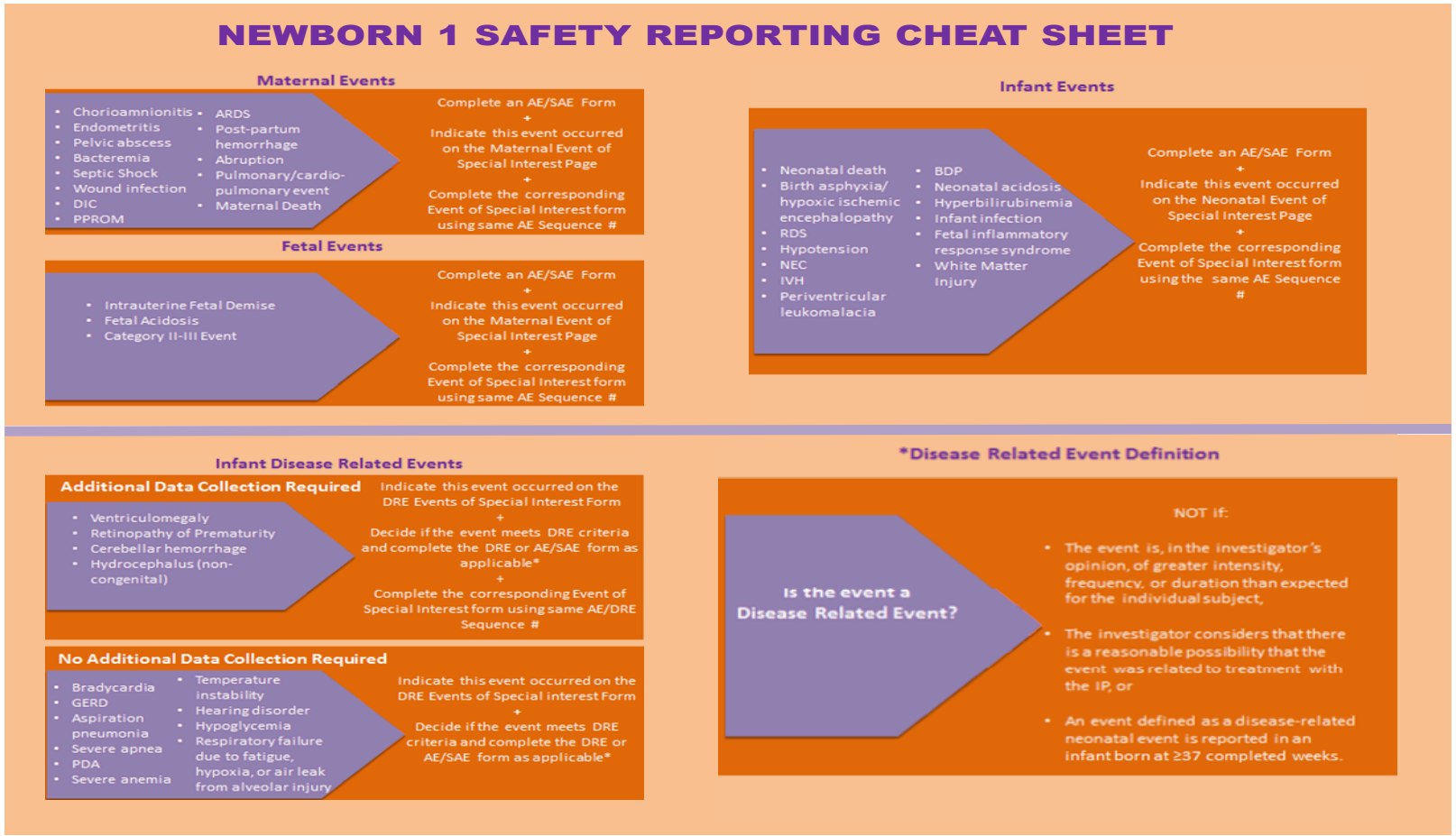
NOTE: Information collected from the time of birth through 28 days post EDD.

Neonatal AEs of special interest are defined by their relationship to maternal chorioamnionitis and will include the following:

- Neonatal death
- Asphyxia
- Infections (early onset neonatal sepsis, septic shock, pneumonia, meningitis)
- RDS
- Hypotension
- Intraventricular hemorrhage/periventricular leukomalacia with cysts or porencephaly
- Bronchopulmonary dysplasia

- Neonatal acidosis
- Hyperbilirubinemia
- Necrotizing enterocolitis (any modified Bell's staging criteria)
- Hypoxic ischemic encephalopathy

12.5. Appendix 5: Safety Reporting Cheat Sheet



AE = adverse event; ARDS = adult respiratory distress syndrome, BDP = bronchopulmonary dysplasia; DIC = Disseminated Intravascular Coagulation; DRE = disease-related event; GERD = gastroesophageal reflux disease, IP = investigational product; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; RDS = respiratory distress syndrome; SAE = serious adverse event.

12.6. Appendix 6: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and

- Response to medicine, including retosiban or any concomitant medicines;
- Preterm labor susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will use data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a reporting and analysis plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- Two blood samples will be taken for DNA extraction: one for maternal DNA (at all participating investigational centers) and one for cell-free fetal DNA (at US and Canadian investigational centers only). These samples will be collected at the screening visit, after the subject has provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample(s) are described in the laboratory manual. The DNA from the sample(s) may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample(s), then the sample(s) may be destroyed. The genetic samples are collected on a single occasion unless a duplicate sample is required due to an inability to use the original sample(s).

The genetic sample(s) is labeled (or “coded”) with the same study-specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

The need to conduct genetic analysis may be identified after a study (or a set of studies) of retosiban has been completed and the clinical study data are reviewed. In some cases, the samples may not be studied, e.g., no questions are raised about how people respond to retosiban or other treatment.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample(s) be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being collected.

Subject Withdrawal From Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample(s), if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample(s) is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample(s)

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the time frame specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data have not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Subjects Who Do Not Receive Study Treatment

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.7. Appendix 7: Cytochrome P450 3A4 Enzyme Inhibitors and Inducers

Medications that are considered cytochrome P450 3A4 enzyme (CYP3A4) inducers and inhibitors are permitted; however, concomitant administration of strong CYP3A4 inducers or strong inhibitors with the investigational product requires an adjustment to the retosiban dosing regimen (see Protocol Section 6.3.2).

Following is a list of CYP3A4 inhibitors and inducers, each classified as strong, moderate, or weak on the basis of changes in the AUCi/AUC (area of the curve of substrate in the presence of an inhibitor/area under the curve of substrate in a control condition). This is not an exhaustive list; the summary of product characteristics and/or the package insert for each concomitant medication should be reviewed to determine if the product is a strong CYP3A4 inducer or inhibitor.

Strong[1] (Requires Adjustment to Dosing Regimen)	Moderate[2]	Weak[3]
Inhibitors		
Amprenavir	Aprepitant	Amlodipine
Atazanavir	Cimetidine	Atomoxetine
Clarithromycin	Darunavir	Atorvastatin
Conivaptan	Diltiazem	Azithromycin
Fosamprenavir	Erythromycin	Bicalutamide
Grapefruit juice[4]	Fluconazole	Chlorzoxazone
Indinavir	Imatinib	Cilostazol
Itraconazole	Nifedipine	Cyclosporine
Ketoconazole	Tofisopam	Darifenacin
Nefazodone	Verapamil	Dasatinib
Nelfinavir		Ezetimibe
Ritonavir		Fentanyl
Saquinavir		Fluvoxamine
Telithromycin		Gemfibrozil
Troleandomycin		Isoniazid

Strong[1] (Requires Adjustment to Dosing Regimen)	**Moderate[2]**	**Weak[3]**
Voriconazole		Lacidipine
		Omeprazole
		Posaconazole
		Propiverine
		Propofol
		Quinidine
		Ranitidine
		Ranolazine
		Roxithromycin
		Tabimorelin
Inducers		
Strong[1] (**Requires Adjustment to Dosing Regimen**)	**Moderate[2]**	**Weak[3]**
Carbamazepine	Bosentan	Aprepitant
Efavirenz	Etravirine	Amprenavir
Phenytoin	Nafcillin	Avasimibe
Rifampin	Nevirapine	Dexamethasone
St. Johns Wort	Phenobarbital	Glycyrrhizin
		Modafinil
		Oxcarbazepine

Strong[1] (Requires Adjustment to Dosing Regimen)	**Moderate[2]**	**Weak[3]**
		Pioglitazone
		Prednisone
		Rifabutin
		Rufinamide

1. Strong inhibitor: >5 AUCi/AUC (area of the curve of substrate in the presence of an inhibitor/area under the curve of substrate in a control condition); strong inducer: <0.2 AUCi/AUC. Co-administration of study drug with a strong inhibitor or strong inducer requires an adjustment to the study drug dosing regimen.
2. Moderate inhibitor: 2 to 5 AUCi/AUC; moderate inducer: 0.2 to 0.5 AUCi/AUC.
3. Weak inhibitor: <2 AUCi/AUC; weak inducer: 0.5 to 0.8 AUCi/AUC.
4. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. However, no dose adjustment is needed for retosiban, as grapefruit juice is not expected to cause an interaction given that retosiban is administered intravenously.

12.8. Appendix 8: Country-Specific Requirements

At US and Canadian investigational centers only:

One maternal blood sample will be taken for DNA extraction to provide cell-free fetal DNA. This sample will be collected at the screening visit, after the subject has provided informed consent for genetic research (see Section 7.10 and Appendix 5).

12.9. Appendix 9: Protocol Changes

Protocol Amendment Number 01

Protocol Amendment Number 01 is applicable to all clinical study centers participating in this study. Protocol changes specified in Amendment Number 01 are summarized as follows:

- Revised the time-to-delivery co-primary endpoint into a composite endpoint consisting of (1) time to delivery or (2) time to treatment failure, whichever occurs first. The inclusion of time to treatment failure in the co-primary endpoint resulted from advice from the US Food and Drug Administration (FDA), where it was considered equally important to evaluate treatment effect in the context of the investigator's decision to use tocolytic treatment for the subject's clinical management. Treatment failure will be defined as the administration of any putative tocolytic medication, such as calcium-channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), or β-agonists during the course of the study and will be considered to have occurred in the following situations:
    - Administration of a tocolytic following investigational product (IP) discontinuation during the Inpatient Randomized Treatment Phase
    - Administration of a tocolytic in an undelivered subject for the management of recurrent preterm labor
    - Use of maintenance tocolysis is prohibited (Section 6.11.2.1); however, any subject treated with a tocolytic as maintenance treatment during the Post-infusion Assessment Phase will be considered a treatment failure.
- Revised the description of the study design to remove any implication or impression that magnesium sulfate was a required treatment. The protocol now indicates that investigators have discretion to use a standardized regimen of magnesium sulfate. Likewise, the protocol emphasizes that investigators have discretion to use intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection. Given the allowance for these discretionary treatments, the study design no longer is considered consistent with the International Conference on Harmonisation guidance E10 (Choice of Control Group) description of an add-on design. As a result, references to an add-on design have been removed from the protocol and the study design is described as a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study.
- Revised the protocol to stipulate that magnesium sulfate should be administered as a standardized regimen if the investigator elects to use magnesium sulfate for the subject's clinical management. The protocol previously allowed the investigator to determine the magnesium sulfate regimen. Recognizing that a number of different dosing regimens exist for the use of magnesium sulfate in obstetrics, the magnesium sulfate regimen has been standardized in order to avoid wide variations in the magnesium sulfate dose given to subjects. The intravenous magnesium sulfate regimen consists of a 4 to 6 g loading dose and 1 to 2 g/hour infusion rate not to exceed 48 hours.

- Revised the protocol to stipulate that antenatal corticosteroid treatment should be administered as either two 12-mg doses of betamethasone given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone every 12 hours administered intramuscularly, if treatment has not been given within 7 days of study enrollment. Similar to magnesium sulfate, the change is based on the need to standardize the betamethasone or dexamethasone regimen in order to control for wide variations in the antenatal corticosteroid doses.
- Added the secondary endpoints of (1) time to delivery, (2) time to treatment failure, and (3) proportion of women receiving any putative tocolytic. These endpoints allow for an assessment of treatment effect on the individual components of the composite co-primary endpoint, time to delivery or treatment failure.
- Revised the guidance regarding an adequate treatment response to be more consistent with obstetric practice. An adequate treatment response was previously based on a clinically relevant reduction in the frequency of contractions without an increase in cervical dilation. Investigators have noted that the clinical assessment of response is not necessarily limited to contraction frequency and cervical dilation. As a result, the protocol now indicates the investigator can assess treatment response on the basis of contraction frequency and/or intensity or cervical examination, including dilation, effacement, and station. An adequate response is now based on (1) a clinically relevant reduction of contraction frequency and/or intensity or (2) no change in the cervical examination.
- Added the volume of maternal blood that will be collected for (1) hematology, chemistry, and liver function tests; (2) biomarker analyses, (3) genetic analyses, and (4) pharmacokinetic analyses, as well as the amount of umbilical cord blood that will be collected for pharmacokinetic analysis in subjects who deliver within 12 hours of IP exposure.
- Added guidance to investigators to carefully monitor the total volume of oral and intravenous fluid administered during preterm labor management to avoid excessive fluid intake and risks for maternal and/or neonatal dilution hyponatremia or pulmonary edema.
- Removed the requirement to collect a placental tissue sample for pathologic examination when delivery occurred at an investigational center. Limiting the collection of placental pathology samples to investigational centers has the potential to confound the analysis through selection bias.
- Removed the requirement to collect cord blood samples for biomarker and genetic testing when delivery occurred at an investigational center. Limiting collection of cord blood samples to investigational centers has the potential to confound the analysis through selection bias.
- Added the requirement for US and Canadian investigational centers to collect a maternal blood sample for cell-free fetal DNA in women who provide informed consent for genetic research. The maternal blood sample will be collected during the Screening Phase, therefore removing concern about selection bias associated with cord blood samples collected at delivery.

- Clarified that any SAEs and AEs of special interest that are unresolved at 28 days post EDD should be followed to stabilization or resolution in those infants participating in the follow-up study.
- Revised the protocol to prohibit the use of calcium-channel blockers, nonsteroidal anti-inflammatory drugs, and β-agonists for tocolysis during IP administration or for maintenance tocolysis in subjects who remained undelivered following the Inpatient Treatment Phase. Because the use of any putative tocolytic medication defines a subject as a treatment failure under the revised co-primary endpoint, it is critical for investigators to avoid concomitant use of tocolysis during IP administration or the use of maintenance tocolysis.
- Changed the methodology to be used to control the Type I error for the planned interim analyses, such that the O'Brien-Fleming boundaries to be used at the second interim analysis and final analysis will be based on the actual information fraction (i.e. the ratio of the actual sample size at the second interim analysis and the re-estimated final sample size). he change resulted from feedback from the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) Scientific Advice and subsequent review of the Paediatric Investigation Plan (PIP) modification by the Paediatric Committee (PDCO).
- Modified the statistical adjustment for the interim analyses such that the O'Brien-Fleming boundary to be used at the 2nd interim will be based on the actual information fraction (i.e. using the re-estimated final sample size) rather than on a fixed information fraction.
- Modified the hypotheses, sample size, interim analyses and primary analyses section to reflect the change in the co-primary endpoint of time to delivery or treatment failure. The key secondary analyses section was also modified to reflect the inclusion of time to delivery as a key secondary endpoint.
- Added magnesium sulfate use and tocolytic use following IP discontinuation as subgroups for comparison of retosiban versus placebo for the co-primary and key secondary endpoints. The addition of these subgroups is based on protocol changes in which the use of magnesium sulfate is discretionary and the use of a tocolytic subsequent to IP discontinuation defines a treatment failure.
- Incorporated other administrative changes. The rationale for these changes is to ensure a clear and complete protocol for use at the investigational centers.

Specific Changes in the Text

Title page:

Randomized, Double-blind, Multicenter, Phase III Study Comparing the Efficacy and Safety of Retosiban Versus Placebo ~~as Add-on Therapy~~ for Women in Spontaneous Preterm Labor

Authors (GSK): PPD

Authors (PPD): PPD

Author (Parexel): PPD

Synopsis, Rationale:

This study (NEWBORN-1) aims to show that retosiban provides additional neonatal benefit through its effect to arrest labor and prolong pregnancy sufficiently to allow for fetal maturation without **significant** increased risk to the fetus or neonate. Clinical validation of the relationship between prolongation of pregnancy and neonatal benefit would establish retosiban as the first drug to add benefit to that of the well-established benefits of antenatal corticosteroids for this indication.

Synopsis, Objectives/Endpoints:

Objectives	Endpoints
Primary	
• To demonstrate the superiority of retosiban to prolong pregnancy and improve neonatal outcomes compared with placebo	• Time to delivery **or treatment failure, whichever occurs first** • Proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite determined up to 28 days after the estimated date of delivery of

Synopsis, Overall Design:

- NEWBORN-1 is a Phase III, randomized, double-blind, **placebo-controlled,** parallel-group, multicenter study
- Eligible subjects will be randomly assigned in a 1:1 ratio to receive either retosiban IV infusion over 48 hours or **matched** placebo IV infusion over 48 hours
- ~~The study will use an add-on design, in which subjects are randomly assigned to treatment with retosiban or placebo in addition to the following treatments, administered in accordance with institutional guidelines: (1) antenatal corticosteroid treatment; (2) magnesium sulfate for fetal neuroprotection; AND/OR (3) magnesium sulfate for tocolysis (details provided in the protocol)~~
- **Antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours, if treatment has not been given within 7 days of study enrollment. Investigators have discretion to use a standardized regimen of magnesium sulfate, as well as intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection.**
- Prior to randomization, each subject will be stratified by progesterone treatment at Screening (subjects on established progesterone therapy vs subjects not on

established progesterone therapy) and GA ($24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$, or $31^{0/7}$ to $33^{6/7}$)

Synopsis, Treatment Arms and Duration

- NEWBORN-1 will comprise 6 phases: Screening, Inpatient Randomized Treatment, Post-Infusion Assessment, Delivery, Maternal Post-Delivery Assessment, and Neonatal Medical Review. The duration of any subject's (maternal or neonatal) participation in the study will be variable and dependent on GA at study entry and the date of delivery
- Retosiban treatment will be administered as a 6-mg IV loading dose over 5 minutes followed by a 6-mg/hour continuous infusion ~~over 48 hours~~ **for the remainder of the 48-hour treatment period**. ~~An adequate treatment response is defined as a clinically relevant reduction in the frequency of contractions without an increase in cervical dilation~~
- The placebo control will be a normal saline (0.9% sodium chloride) infusion matched **for the retosiban volume**, ~~for the~~ **IV** loading dose **over 5 minutes**, and continuous infusion ~~rates, including a dose increase in subjects with an inadequate response after the first hour of treatment for the~~ **rate for the remainder of the 48-hour treatment period**.
- **An adequate response is based on (1) a clinically relevant reduction of contraction frequency and/or intensity or (2) no change in the cervical examination.**
- Subjects with an inadequate response **any time** after the first hour of treatment will be administered another 6-mg **retosiban or matched placebo** loading dose and the **retosiban or matched placebo** infusion rate will be increased to 12 mg/hour for the remainder of the 48-hour treatment period.
- At each of the 2 planned interim analysis, all available safety and efficacy data will be reviewed by the unblinded independent data monitoring committee who may make recommendations to terminate the study based on prespecified **criteria or at any time for an unfavorable benefit:risk profile**

Synopsis, Analysis

The primary comparison of interest is retosiban versus placebo for the co-primary endpoints: time to delivery **or treatment failure, whichever occurs first,** and neonatal composite ~~outcome~~ **endpoint**. The statistical analysis will test the null hypothesis in the Intent-to-Treat Population that there is no difference between retosiban and placebo versus the alternative hypothesis that there is a difference between the 2 co-primary endpoints.

Section 2, Introduction

In contrast, results from the OTA10256 Phase II placebo-controlled study found that retosiban prolonged pregnancy and reduced prematurity rates in women between $30^{0/7}$ and $35^{6/7}$ weeks' gestation. Retosiban, given intravenously over 48 hours, increased days to delivery by a mean of 8.2 days relative to placebo; this difference was consistent across GAs (Figure 1). The incidence of birth prior to 37 weeks' gestation in the retosiban group was 18.7% compared with 47.2% in the placebo group (see the investigator's brochure [IB] Section 5.3.2.2.2 **[GlaxoSmithKline Document Number CM2006/00201/03])**. No placebo controlled tocolytic studies have demonstrated an effect of this magnitude in spontaneous preterm labor. External experts have generally agreed that prolonging the time to delivery by 1 week in the absence of harm may benefit the newborn, particularly in women who experience spontaneous preterm labor at early GAs.

The emerging safety profile for retosiban also appears favorable. All reported adverse events (AEs) (maternal, fetal, and neonatal) were generally similar to placebo or consistent with expected events in the population under study. A summary of the complete results for Study OTA105256 is included in the IB (Section 5.3.2.1 **[GlaxoSmithKline Document Number CM2006/00201/03]**).

This study (NEWBORN-1) aims to show that retosiban provides additional neonatal benefit through its effect to arrest labor and prolong pregnancy sufficiently to allow for fetal maturation without **significant** increased risk to the fetus or neonate. Clinical validation of the relationship between prolongation of pregnancy and neonatal benefit would establish retosiban as the first drug to add benefit to that of the well-established benefits of antenatal corticosteroids for this indication.

Section 2.2., Brief Background

Oxytocin is a potent uterotonic whose role in the initiation and progression of human labor, both term and preterm, has been actively investigated for many years. Although preterm labor may well be a syndrome with various etiologies, oxytocin action on the uterus likely represents a common step in activation of the myometrium. Paracrine rather than endocrine mechanisms ~~are thought to~~ **may** mediate this process, in which the effects of oxytocin are governed by tissue-specific oxytocin receptor expression, which leads to direct contractile effects in myometrium and prostaglandin formation in the decidua. Prostaglandins in turn mediate myometrial contractions and cervical ripening [Fuchs, 1982; Benedetto, 1990].

Section 3., Objectives and Endpoints

Objectives	Endpoints
Primary	

• To demonstrate the superiority of retosiban to prolong pregnancy and improve neonatal outcomes compared with placebo	• Time to delivery **or treatment failure, whichever occurs first. Time to delivery will be calculated** from the start of study treatment administration until delivery. **Time to treatment failure will be calculated from the start of study treatment administration to the administration of any putative tocolytic medication**
	• Proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite determined up to 28 days after the estimated date of delivery (EDD) of $40^{0/7}$ weeks:
	  • Fetal or neonatal death
	  • Respiratory distress syndrome (RDS)
	  ○ Requiring continuous positive airway pressure or mechanical ventilation. Diagnosis requires a chest radiograph consistent with RDS (reticulogranular appearance to the lung fields or air bronchograms) within the first 24 hours of life, OR
	  ○ Received surfactant for a clinical picture of RDS within the first 24 hours of life
	  • Bronchopulmonary dysplasia at ≥36 weeks postmenstrual age (determined by adding chronological age to GA at delivery), defined as follows:
	  ○ >21% supplemental oxygen requirement, OR
	  ○ Use of high-flow nasal cannula at ≥1 L (21% oxygen)
	  • Necrotizing enterocolitis or isolated perforation
	  ○ Diagnosed by radiographic evidence of Stage II or higher according to Bell's staging criteria (fixed/unchanging bowel loops, pneumatosis intestinalis, portal venous gas, pneumoperitoneum),

Objectives	Endpoints
	OR ○ Pneumatosis intestinalis, bowel necrosis, or perforation noted at surgery • Sepsis based on positive blood culture with clinical features of sepsis • Meningitis based on positive results for cerebrospinal fluid culture performed as part of infection workup • Retinopathy of prematurity ○ Confirmed by an ophthalmologist based on international committee Stage 4 or 5, OR ○ Requiring surgical treatment with laser or other surgical intervention including cryotherapy or treatment with antivascular endothelial growth factor • Intraventricular hemorrhage (IVH) ○ Grade 3 or 4 (severe IVH), OR ○ Any grade of IVH with posthemorrhagic hydrocephalus requiring a shunt • White matter injury, documented on cranial ultrasound or magnetic resonance imaging, as indicated by the following: ○ Multiple cystic lucencies in periventricular white matter (may be bilateral or unilateral, may vary in size, and be diffuse or focal in distribution), OR ○ Porencephalic cyst (not including subependymal or choroid plexus cysts), OR ○ Persistent ventriculomegaly, moderate to severe • Cerebellar hemorrhage (unilateral or bilateral)
	Supportive Key Secondary
	• **<u>Time to delivery</u>** • Proportion of births prior to $37^{0/7}$ weeks' gestation • Proportion of births at term ($37^{0/7}$ to $41^{6/7}$ weeks' gestation) • Length of neonatal hospital stay

Objectives	Endpoints
	Supportive Other Secondary
	• Proportion of births prior to $32^{0/7}$ weeks' gestation • Proportion of births prior to $28^{0/7}$ weeks' gestation • Proportion of births ≤7 days • Proportion of births ≤48 hours • Proportion of births ≤24 hours • Proportion of neonates with any of the co-primary composite neonatal morbidity and mortality, excluding RDS • Proportion of neonates with each individual component of the composite neonatal morbidity and mortality endpoints • Neonatal admission to a specialized care unit and length of stay • Newborn hospital readmission and length of stay • Ambulatory surgery • **Time to treatment failure** • **Proportion of women receiving any putative tocolytic**
Secondary	

• To describe the maternal, fetal, and neonatal safety profile during and after IV retosiban treatment compared with placebo	Maternal:
	• Incidence of reported AEs and serious AEs (SAEs)
	• Significant changes in vital signs and clinical laboratory tests
	• Incidence of clinical and laboratory toxicities causing subject to discontinue study treatment
	• Incidence of women scoring 12 or higher on the Edinburgh Postnatal Depression Scale (EPDS)
	• Maternal AEs of special interest
	  • Maternal death
	  • Chorioamnionitis and its complications
	  ○ Clinical chorioamnionitis, preterm premature rupture of membranes, endomyometritis, wound infection, pelvic abscess, bacteremia, septic shock, disseminated intravascular coagulation, and adult RDS
	  • Placental abruption

Objectives	Endpoints

	• Postpartum hemorrhage – postpartum hemorrhage and/or retained placenta
	• Pulmonary edema
	Fetal:
	• Incidence of reported AEs and SAEs
	• Fetal acidosis
	• Fetal AEs of special interest
	  • Intrauterine fetal demise
	  • Category II or III fetal heart rate tracing (defined according to ACOG Practice Bulletin 106 [ACOG Practice Bulletin No. 106, 2009])
	  • Fetal inflammatory response syndrome characterized by cord blood interleukin-6 >11 pg/mL, funisitis, or chorionic vasculitis
	Neonatal:
	NOTE: Information collected from the time of birth through 28 days post EDD.
	• Neonatal Apgar scores (at 1 and 5 minutes after birth),
	• Growth parameters (weight, length, and head circumference) at birth and at discharge
	• Incidence of reported AEs and SAEs
	• Neonatal AEs of special interest will include the following:
	  • Neonatal death
	  • Asphyxia
	  • Infections (early onset neonatal sepsis, septic shock, pneumonia, meningitis)
	  • RDS
	  • Hypotension
	  • IVH/periventricular leukomalacia
	  • Bronchopulmonary dysplasia
	  • Neonatal acidosis
	  • Hyperbilirubinemia
	  • Necrotizing enterocolitis
	  • Hypoxic ischemic encephalopathy

• To determine the effect of retosiban treatment compared with placebo on health care resource use for the maternal and neonatal hospitalizations	• Assess maternal and neonatal health care resource use associated with preterm labor and preterm delivery. Health care resource use of interest include: • Maternal hospital admission (e.g.,

Objectives	Endpoints
	length of stay by hospital unit and type) and resource use (e.g., use of transport services and admission to extended stay facility) • Neonatal interventions of interest (e.g., parenteral nutrition, surfactants, blood products), procedures (e.g., imaging, such as ultrasound and computed tomography), and surgical procedures • Neonatal hospital admission (e.g., length of stay by hospital unit and type) and resource use (e.g., use associated with neonatal comorbidities of interest).
• To obtain further data on the pharmacokinetics of retosiban in pregnant women, including the effect of covariates such as age, weight, race/ethnicity, and GA on retosiban clearance and volume of distribution	• Retosiban clearance and volume of distribution and the effect of covariates on these parameters

Section 4.1., Overall Design

NEWBORN-1 is a Phase III, randomized, double-blind, parallel-group, **placebo-controlled,** multicenter study. This study will be conducted in approximately 900 females, aged 12 to 45 years, with an uncomplicated, singleton pregnancy and intact membranes in preterm labor between $24^{0/7}$ and $33^{6/7}$ weeks of gestation. Eligible subjects (for the purposes of this protocol, subject refers to the mother and not the infant unless otherwise stated) will be randomly assigned in a 1:1 ratio to receive either retosiban IV infusion over 48 hours or **matched** placebo IV infusion over 48 hours (approximately 450 subjects in each group).

~~The study will use an add-on design, in which subjects are randomly assigned to treatment with retosiban or placebo in addition to the following treatments:~~

- ~~Antenatal corticosteroid treatment: Investigators should administer either betamethasone or dexamethasone for fetal maturation in accordance with institutional guidelines,~~
- ~~Magnesium sulfate for fetal neuroprotection: Investigators who believe magnesium sulfate is an important component of care to improve neonatal outcome have the option to use magnesium sulfate for fetal neuroprotection in accordance with institutional guidelines,~~

  ~~AND/OR~~

- ~~Magnesium sulfate for tocolysis: Investigators can administer magnesium sulfate for up to 48 hours as an adjunctive treatment to support antenatal corticosteroid therapy. Magnesium sulfate tocolysis can be discontinued once antenatal corticosteroid treatment is complete or labor subsides, following established guidelines [Mercer, 2009; ACOG Committee Opinion No. 573, 2013]~~

~~Antibiotic treatment for group B streptococcal (GBS) infections is also allowed per institutional guidelines.~~

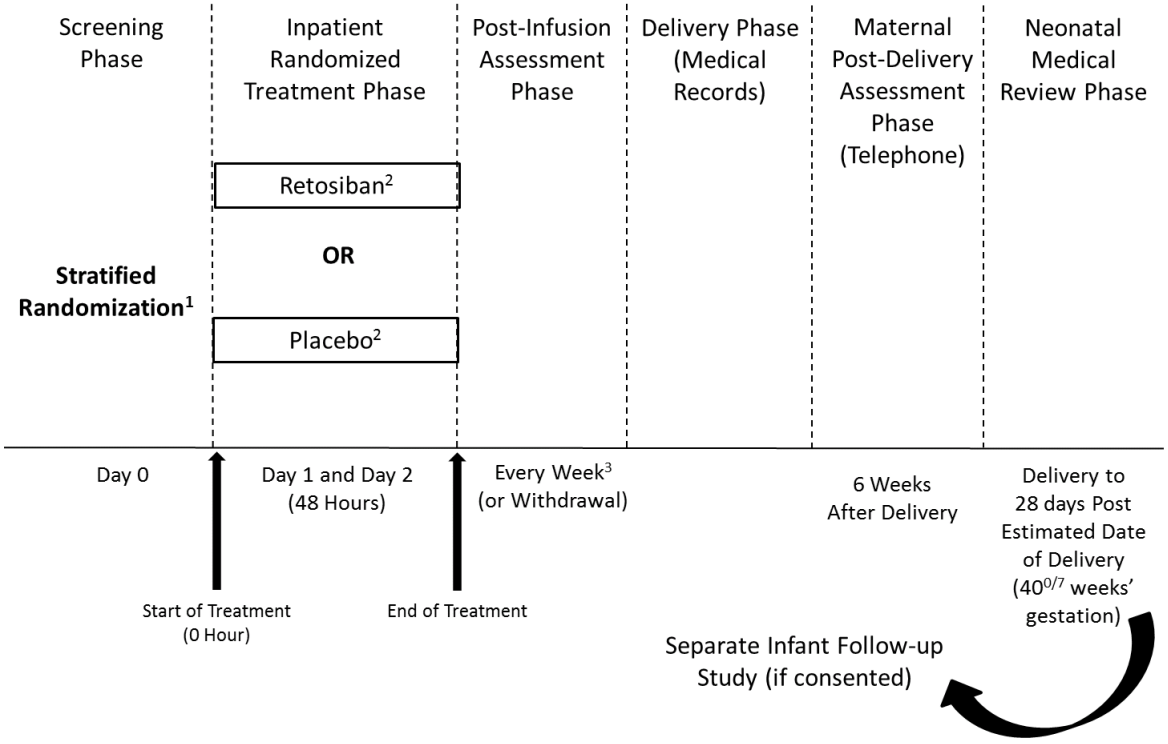
Antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours, if treatment has not been given within 7 days of study enrollment. Investigators have discretion to use a standardized regimen of magnesium sulfate, as well as intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection (for additional details see Section 6.11).

Prior to randomization, each subject will be stratified by progesterone treatment and GA. The progesterone strata will consist of subjects on established progesterone therapy or subjects not on established progesterone therapy at Screening (see Section 6.11.1.3 for details) The GA strata are $24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$, or $31^{0/7}$ to $33^{6/7}$.

All subjects exposed to randomized treatment will be asked to remain in the study through delivery and maternal post-delivery assessments and review of the newborn records. Withdrawal from the study should only occur if a subject either refuses to continue participation or is lost to follow-up (see Section 5.3.1).

Section 4.2., Treatment Arms and Duration

Figure 2, Study Design



1. Stratification (1:1) to retosiban or **matched** placebo based on established progesterone therapy at Screening (subjects on established progesterone therapy versus subjects not on established progesterone therapy) and gestational age ($24^{0/7}$ to $25^{6/7}$; $26^{0/7}$ to $27^{6/7}$; $28^{0/7}$ to $30^{6/7}$; $31^{0/7}$ to $33^{6/7}$).
2. ~~Randomized treatment will be added to existing treatment with antenatal corticosteroids and magnesium sulfate for fetal neuroprotection and/or tocolysis.~~ **Antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours, if treatment has not been given within 7 days of study enrollment. Investigators have discretion to use a standardized regimen of magnesium sulfate, as well as intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection.**
3. Subjects who have not delivered after 48 hours will return for a face-to-face post-infusion visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) after the Inpatient Randomized Treatment Phase. The subject will then be contacted every week via telephone to determine and record if she has delivered or if she has experienced any subsequent episodes of preterm labor. Retreatment with the investigational product (retosiban or placebo) is not allowed.

. . .

Subjects will be randomly assigned to treatment on Day 1 of the Inpatient Randomized Treatment Phase. The treatment phase will be 48 hours. ~~Subjects who do not experience labor progression and remain undelivered after 48 hours will be scheduled for a face to face post-infusion visit for obstetric assessments as part of the Post Infusion Assessment Phase. Detailed summaries of the assessments for each study phase are provided in the Study Procedures Manual (SPM).~~ **Retosiban treatment will be administered as a 6 mg IV loading dose over 5 minutes followed by a 6 mg/hour continuous infusion for the remainder of the 48-hour treatment period. The placebo control will be a normal**

saline (0.9% sodium chloride [NaCl]) infusion matched for the retosiban volume, IV loading dose over 5 minutes, and continuous infusion rate for the remainder of the 48-hour treatment period. The duration of the treatment should not exceed 48 hours.

~~Retosiban treatment will be administered as a 6 mg IV loading dose over 5 minutes followed by a 6 mg/hour continuous infusion over 48 hours.~~ An adequate ~~treatment~~ response is ~~defined as a clinically relevant reduction in the frequency of contractions without an increase in cervical dilation~~ **based on (1) a clinically relevant reduction of contraction frequency and/or intensity or (2) no change in the cervical examination.** ~~For s~~**S**ubjects with an inadequate response **any time** after the first hour of treatment will be administered another 6-mg **retosiban or matched placebo** loading dose and the **retosiban or matched placebo** infusion rate will increased to 12 mg/hour for the remainder of the 48-hour treatment period. A subject's response should be assessed for at least 1 hour following a dose increase before a decision is made to discontinue randomized treatment due to lack of response. ~~The duration of the treatment should not exceed 48 hours and the total dose should not exceed 582 mg.~~

~~The placebo control will be a normal saline (0.9% sodium chloride [NaCl]) infusion matched for the loading dose and continuous infusion rates, including a dose increase in subjects with an inadequate response after the first hour of treatment.~~

Investigators will be required to indicate in the electronic case report form (eCRF) the reason or reasons for a dose increase.

Treatment can be discontinued due to labor progression with imminent delivery, intolerance to treatment, and any contraindication to continuation of randomized treatment. Subjects who discontinue randomized treatment will be asked to remain in the study through the maternal post-delivery assessment and review of the newborn records. Withdrawal from the study should only occur if a subject either refuses to continue or is lost to follow-up.

Subjects who ~~do not experience labor progression and~~ remain undelivered after 48 hours will be scheduled for a face-to-face post-infusion visit for obstetric assessments as part of the Post Infusion Assessment Phase. The visit will be scheduled 1 week (acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase. The subject will then be contacted every week via telephone to determine and record if she has delivered or if she has experienced any subsequent episodes of preterm labor. Retreatment with the investigational product (IP; retosiban or placebo) is not allowed.

~~For those subjects who deliver at the investigative center, a placental tissue sample will be obtained at the time of delivery for both local and central laboratory pathological examination. Additionally, for subjects who deliver at the investigative center, a single cord blood sample will be collected and divided for potential genetic research and biomarker assays. In the event that delivery occurs within 12 hours of IP (retosiban or placebo) completion or discontinuation, the single cord blood sample will also be divided for pharmacokinetic (PK) analysis. Likewise, a breast milk/colostrum sample will be collected for PK analysis in women who deliver and produce breast milk within 12 hours after completion or discontinuation of the IP.~~ Once delivery is confirmed during the

Delivery Phase of the study, the maternal delivery and hospitalization record will be reviewed for data collection by the investigator obstetrician. **If delivery occurs at a different hospital, the investigator obstetrician will need to obtain the maternal delivery and hospitalization record for review. For those subjects who deliver at the investigative center within 12 hours of IP (retosiban or placebo) completion or discontinuation, a cord blood sample will be collected for pharmacokinetic (PK) analysis. Likewise, a breast milk/colostrum sample will be collected for PK analysis in women who deliver at the investigative center and produce breast milk within 12 hours after IP completion or discontinuation.**

. . .

Detailed summaries of the assessments for each study phase are provided in the Study Procedures Manual (SPM).

Two interim analyses are planned. The first interim analysis will occur after approximately 150 women/newborn pairs complete all assessments. The second interim analysis will occur after approximately 400 women/newborn pairs complete all assessments. At each interim analysis, all available safety and efficacy data will be reviewed by the unblinded independent data monitoring committee (IDMC) who may make recommendations to terminate the study based on prespecified criteria. At the second interim analysis, the IDMC may also make recommendations to increase the sample size of the study based on prespecified criteria. **Additionally, the IDMC may make recommendations to terminate the study at any time for an unfavorable benefit:risk profile.** Subjects will continue to be enrolled while the interim analyses are being conducted.

Section 4.4., Design Justification

As discussed in Section 2, there is no convincing evidence that current tocolytic regimens sufficiently prolong pregnancy to provide neonatal benefit beyond that of antenatal corticosteroids alone. In contrast, results from a Phase II placebo-controlled study suggest that retosiban's effect to prolong pregnancy may be sufficient to improve neonatal outcomes. In women with spontaneous preterm labor between $30^{0/7}$ to $35^{6/7}$ weeks' gestation, retosiban administered intravenously over 48 hours increased time to delivery by a mean of 8.2 days above and beyond that of placebo; this difference was consistent across GAs. Further, there is general agreement that prolonging the average time to delivery by 1 week in the absence of significant risk is likely to benefit the newborn, particularly in women who present in spontaneous preterm labor at early GAs. Together, these findings form the basis of the clinical hypothesis, which states that retosiban provides neonatal benefit beyond that of antenatal corticosteroids by prolonging pregnancy sufficiently to allow for continuing fetal maturation without causing significant risk to the fetus or neonate. To test this hypothesis, the study uses a randomized design that compares retosiban with placebo when both are added to antenatal corticosteroid treatment for fetal maturation and magnesium sulfate treatment for fetal neuroprotection or tocolysis.

~~The study population represents a particularly vulnerable group for poor infant outcomes, for whom effective treatment options are limited. As a result, the protocol allows~~

~~investigators discretion for the use of betamethasone or dexamethasone in accordance with institutional guidelines. Antenatal corticosteroids have been proven to reduce the risks for neonatal mortality and morbidity and are recommended in women between 24 weeks and 34 weeks' gestation at risk for spontaneous preterm birth [ACOG Practice Bulletin No. 127, 2012; RCOG Green top Guideline No. 7, 2010). Investigators have the option of using magnesium sulfate for tocolysis according to institutional guidelines in order to administer antenatal corticosteroids. Although there is no evidence that magnesium sulfate tocolysis improves neonatal outcomes [Mercer, 2009], short-term use of magnesium sulfate to prolong pregnancy for administration of antenatal corticosteroids in pregnant women between 24 and 34 weeks of gestation at risk of preterm delivery is appropriate [ACOG Committee Opinion No. 573, 2013]. Investigators will also have discretion to use magnesium sulfate for fetal neuroprotection according to institutional guidelines. Fetal neuroprotection is becoming a component of obstetric care based on the available evidence indicating magnesium sulfate given prior to anticipated early preterm birth reduces the risk of cerebral palsy [ACOG Committee Opinion 455, 2010; Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel, 2010; RCOG Scientific Impact Paper No. 29, 2011b; Society of Obstetricians and Gynaecologists of Canada; SOGC Clinical Practice Guideline 258, 2011]. The potential benefit of these therapies to a high risk obstetric population forms the basis for permitting their use under the add-on design.~~

Placebo-controlled studies provide scientific rigor through their effect to distinguish an effective treatment from an ineffective treatment by controlling for all potential influences on the actual or apparent course of the disease or condition other than those arising from the pharmacologic action of the test drug. Such influences include the natural history of the disease or condition, subject or investigator expectations, use of other therapy, and subjective elements of diagnosis or assessment.

The study population represents a particularly vulnerable group for poor infant outcomes, for whom effective treatment options are limited. As a result, the protocol allows for the use of antenatal corticosteroids, either betamethasone or dexamethasone, magnesium sulfate in a standardized regimen, and intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection.

To fulfill regulatory requirements to study pediatric subjects, pregnant adolescents aged 12 to 17 years are allowed to participate in this study. Adolescent pregnancy is complicated by a higher likelihood of preterm labor and subsequent delivery, but there is no evidence that the pathophysiology of spontaneous labor and delivery differs between pregnant adolescents and adults or that the clinical course differs. Pregnant adolescents are more likely to deliver a low birth weight or preterm infant than older females (<40 years), and their babies have a higher risk of dying during infancy [Mathews, 2010; Martin, 2012]. Since local laws, customs, and institutional practice vary globally, investigator discretion in the enrollment of pediatric subjects is permitted.

~~The add-on design with placebo control represents a reasonable and scientifically valid study design, which gives the investigator discretion to provide antenatal corticosteroids for fetal maturation and magnesium sulfate treatment for fetal neuroprotection and/or~~

~~tocolysis in a vulnerable, at risk population while testing the superiority of retosiban to provide neonatal benefit beyond that of antenatal corticosteroids.~~

~~The add-on design with placebo control is also consistent with International Conference on Harmonisation (ICH) Guidance E10, Choice of Control Group, which notes that such a design has the advantage of providing evidence of improved clinical outcomes, particularly when alternative treatments are not fully effective. This guidance is relevant because current tocolytic drugs fail to provide neonatal benefit beyond that of antenatal corticosteroids and prematurity complications remain disproportionately high in this target population despite antenatal corticosteroids. Further, the add-on design has been used in a variety of therapeutic studies. Recent US Food and Drug Administration drug approvals in which registration studies used an add on design with a placebo control include simeprevir for chronic hepatitis C infection (November 2013), canagliflozin for type 2 diabetes mellitus (March 2013), lacosamide for partial-onset seizures (October 2008), tolvaptan for clinically significant hypervolemic and euvolemic hyponatremia, including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (May 2009), and belimumab for systemic lupus erythematosus (March 2011).~~

Section 4.5.1., Retosiban ~~and Matched Placebo~~

Retosiban will be administered as a 6 mg IV loading dose over 5 minutes followed by a 6 mg/hour continuous infusion for 48 hours. An adequate ~~treatment~~ response is ~~defined as a clinically relevant reduction in the frequency of contractions without an increase in cervical dilation~~ **based on (1) a clinically relevant reduction of contraction frequency and/or intensity or (2) no change in the cervical examination**. For subjects with an inadequate response **any time** after the first hour of treatment, investigators should administer another 6 mg loading dose and increase the infusion rate to 12 mg/hour for the remainder of the 48 hour treatment period (see Section 6.1 ~~for additional dosing details~~ **and Section 6.3 for IP administration and dose adjustments, respectively**).

The **proposed** retosiban dosing regimen has been informed ~~by animal studies defining retosiban concentrations for inhibition of myometrial contractions, evaluations of exposure, safety, and tolerability over~~ **primarily by results from the Phase II study (OTA105256) where** a wide range of doses **was evaluated** in ~~healthy subjects and forced titration studies in pregnant~~ women **with preterm labor. In Parts A and B of this Phase II study,** ~~T~~**t**he retosiban regimen ~~is~~ **was** designed to yield a **target concentration range based on preclinical models of preterm labor. Based on interim analysis of Parts A and B, the target** mean steady-state concentration **was refined in Part C** to ~~of~~ 75 ng/mL. The option to double the dose after 1 hour allows for between-subject variability in retosiban pharmacokinetics, receptor density, and half maximal inhibitory concentration (IC50) values. Findings from Study OTA105256 Part C indicate this dosing strategy was successful, as 60% of subjects responded to the 6 mg/hour infusion, whereas 40% of subjects required an increase in the infusion rate to 12 mg/hour. These findings also support the initial 6 mg/hour infusion rate as the lowest effective dose for the majority of subjects, while recognizing that the higher 12-mg/hour infusion rate may be required in subjects failing to respond to the initial infusion rate.

4.5.2. Matched Placebo

~~For the placebo control,~~ **Normal saline** 0.9% NaCl ~~will be~~ administered intravenously **will serve as the placebo control. The normal saline infusion will be** matched for the **retosiban volume, IV** loading dose **over 5 minutes,** and continuous infusion rate~~s~~, including a dose increase in subjects with an inadequate response **any time** after the first hour of treatment (see Section 6.1 ~~for additional dosing details~~ **and Section 6.3 for IP administration and dose adjustments, respectively**).

As discussed in Section 4.4, use of a placebo control serves to distinguish an effective treatment from an ineffective treatment by controlling for all potential influences on the actual or apparent course of preterm labor other than those arising from the pharmacologic effect of retosiban.

~~4.5.2.Antenatal Corticosteroids~~

~~Antenatal corticosteroid treatment reduces severe neonatal complications and death when administered to women between 24 and 34 weeks' gestation at risk for spontaneous preterm birth [Di Renzo, 2006; RCOG Green top Guideline No. 7, 2010; ACOG Committee Opinion 475, 2011]. Investigators should administer either betamethasone or dexamethasone for fetal maturation in accordance with institutional guidelines.~~

~~4.5.3.Magnesium Sulfate~~

~~Practice guidelines for the use of magnesium sulfate for fetal neuroprotection have been developed by the ACOG Committee on Obstetric Practice and Society for Maternal Fetal Medicine [ACOG Committee Opinion 455, 2010], the Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel [Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel, 2010], and SOGC [SOGC Clinical Practice Guideline 258, 2011]. As these practice guidelines vary according to interpretation and generalizability of the available evidence for the effect of magnesium sulfate given prior to anticipated early preterm birth to reduce the risk of cerebral palsy, investigators electing to administer magnesium sulfate for fetal neuroprotection should consider using 1 of the 3 regimens detailed in published guidelines [ACOG Committee Opinion 455, 2010; Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel, 2010; SOGC Clinical Practice Guideline 258, 2011].~~

~~Magnesium sulfate may also be given as tocolysis for up to 48 hours as an adjunctive treatment to support antenatal corticosteroid therapy. Magnesium sulfate tocolysis can be discontinued once antenatal corticosteroid treatment is complete or labor subsides, following established guidelines [Mercer, 2009; ACOG Committee Opinion No. 573, 2013].~~

Section 4.6.1., Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Fetal exposure through placental transfer	Preclinical data indicate very minimal, if any, maternal CNS penetration or placental transfer of retosiban as supported by the following: In pregnant monkeys there was no detectable retosiban in the cord blood when mothers were dosed up to 100 mg/kg (approximately 7 times the human exposure). However, approximately 4% of circulating drug was detected in the cord blood when mothers were dosed at 300 mg/kg (approximately 24-fold the human exposure). Retosiban is a substrate of P-gp and breast cancer resistant protein transporters, which are thought to play a role in keeping xenobiotics out of the CNS and out of the fetal blood, thereby limiting fetal exposure to retosiban. In reproductive toxicology studies in pregnant monkeys, there were no adverse mother and infant behavioral or locomotor effects observed that were suggestive of CNS toxicity. In rodent neurobehavioral safety studies, there were no adverse clinical signs observed at doses up to 1000 mg/kg.	Analysis of maternal blood and cord blood samples will be performed to test for levels of retosiban in women who deliver at an investigative center within 12 hours of the completion or discontinuation of study treatment infusion in this study. Surveillance for signals indicating adverse fetal or neonatal effects with in utero exposure to retosiban will be performed throughout this study. Infants exposed to retosiban in utero will be followed for ~~a minimum of 24 months~~ **up to 5 years** in a separate follow-up study to assess **long-term** safety and neurodevelopmental outcomes.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
. . .		•
Adverse maternal, fetal, or neonatal outcomes due to prolonging pregnancy in the presence of subclinical intrauterine infection	The study population includes women, particularly those presenting in labor prior to $30^{0/7}$ weeks of gestation, in whom intrauterine infection is implicated as a major etiologic factor. Infection may be chronic and asymptomatic with the first indication being preterm labor or rupture of the membranes. The asymptomatic nature of intrauterine infection, including lack of fever, abdominal pain, and fetal tachycardia, makes the diagnosis challenging. Infection is thought to trigger the labor process as a protective means for both the mother and baby [Goldenberg, 2002].	The protocol will exclude women with a temperature >100.4°F (38°C) for more than 1 hour or ≥101°F (38.3°C), as well as women with confirmed or suspected contraindication for continuation of pregnancy, such as chorioamnionitis, premature rupture of membranes, and abruption. ~~Placental tissue samples will be collected when delivery occurs at an investigative center to examine safety and efficacy outcomes in subjects with subclinical intrauterine infection based on histopathologic examination.~~ A set of AEs of special interest identified in the literature as linked to maternal clinical or subclinical infection has been generated and will be used to collect targeted information of these AEs. This information~~, as well as the results from the histopathology of the placenta data,~~ will be monitored in stream by an IDMC. The unblinded IDMC will review all available safety and efficacy data.
Potential drug-drug interaction with inhibitors of BCRP or P-gp	Retosiban is a substrate of murine BCRP and P-gp *in vitro*. Inhibitors of BCRP and P-gp have the potential to increase exposure of retosiban when co-administered. BCRP and P-gp is expressed in placental membranes and the blood-brain barrier, and there is the potential of increased maternal CNS and fetal exposure to retosiban when co-administered with inhibitors. Clinical experience with exposures 10-fold higher than the exposure at the planned therapeutic dose has shown retosiban to be safe and well tolerated, with no observed untoward effects in adult women of childbearing potential.	Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure. The impact of concomitant use of retosiban with inhibitors of BCRP or P-gp will be assessed through AE monitoring. Analysis of maternal serum and cord blood samples will be performed when delivery occurs within 12 hours of study treatment infusion with co-administration of a BCRP or P-gp inhibitor to assess the effect of P-gp inhibition on placental transfer of retosiban.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Pulmonary edema	Pulmonary edema is a rare but potentially life-threatening complication of pregnancy. In the setting of preterm labor, pulmonary edema is thought to involve both increased hydrostatic pressure and altered vascular permeability. Factors associated with pulmonary edema include spontaneous preterm labor, multifetal pregnancy, chorioamnionitis, pre-eclampsia, cardiac disease, fluid overload, blood transfusion, corticosteroid therapy, and tocolytic treatment. Magnesium sulfate is implicated especially when additional risk factors are present. Randomized studies have not shown an increased risk of pulmonary edema or other serious maternal complications with antenatal magnesium sulfate [Doyle, 2009; Conde-Agudelo, 2009; Bain, 2013]. A retrospective chart review showed that contributing factors for pulmonary edema during magnesium sulfate treatment included high dose, high infusion rate, high net positive fluid balance, concomitant tocolysis, and multifetal gestations [Samol, 2005].	Women with identified risk factors for pulmonary edema are excluded from the clinical study. These include multifetal pregnancies, pre-eclampsia, chorioamnionitis, and certain pre-existing cardiovascular conditions. ~~Guidance is provided to investigators regarding appropriate duration, therapy, and~~ **Magnesium sulfate will be administered in a standardized regimen per the investigator's discretion (see Section 6.11.1.2). Additional information** regarding monitoring of magnesium sulfate ~~for neuroprotection and/or tocolysis (detailed in the therapy~~ **is provided in** SPM~~).~~ Guidance is provided to investigators regarding fluid balance up to the time of starting treatment and for the duration of treatment **(see Section 7.4.8)**. Pulmonary edema is designated as an AE of special interest requiring the collection and/or assessment of specific, relevant history and physical examination findings, targeted eCRFs to characterize any reported events, and a maximum duration of tocolytic treatment with magnesium sulfate of 48 hours.

AE = adverse event; BCRP = breast cancer resistance protein; CNS = central nervous system; eCRF = electronic case report form; IDMC = independent data monitoring committee; P-gp = P-glycoprotein; PPH = postpartum hemorrhage; SPM = Study Procedures Manual.

Section 4.6.2, Benefit Assessment

Birth prior to 34 weeks' gestation represents roughly 30% of preterm births in the United States, half of which are preceded by spontaneous labor [Martin, 2012; Tucker, 1991; Berkowitz, 1998; Meis, 1998; Goldenberg, 2008]. Premature birth in this group carries a disproportionately high risk for death, neonatal complications, and long-term disabilities. Infants born prior to 32 weeks' gestation die at a rate 72 times that of term infants; the mortality rate for infants born between 32 and 33 weeks' gestation is 7-fold higher [Mathews, 2010]. Surviving infants remain susceptible to both short-term and long-term prematurity complications, resulting from injury to immature organ systems [Stoll, 2010; Saigal, 2008].

~~The benefit of antenatal corticosteroids for fetal maturation and magnesium sulfate for fetal neuroprotection and short term prolongation of pregnancy is available to all subjects in accordance with institutional guidelines.~~

Section 4.6.3., Overall Benefit:Risk Conclusion

~~Despite the proven benefit of antenatal corticosteroids, neonatal mortality and morbidity remain disproportionately high in neonates born prematurely to women who experience spontaneous preterm labor.~~ **Based on** ~~T~~**t**he Phase II ~~program found that~~ **results showing** retosiban treatment significantly increased the time to delivery and reduced preterm births, **this study will test whether** ~~These findings suggest the potential for~~ retosiban ~~to~~ **can** ~~provide additional~~ benefit by **prolonging pregnancy and** allowing for continued maturation of fetal organs and systems.

~~Taking into account the~~ **Although experience in pregnant women is limited, the retosiban safety profile is favorable, and no clinical or preclinical safety issues have been identified that preclude further development. In addition, the protocol institutes a number of** ~~incorporated to minimize risk to~~ measures **aimed at mitigating potential risks to** subjects participating in this study ~~including antenatal corticosteroid treatment for fetal maturation and magnesium sulfate for fetal neuroprotection and/or tocolysis, the~~. **These include extensive maternal, fetal, and neonatal safety assessments and an IDMC to monitor maternal, fetal, and neonatal safety in an ongoing manner throughout the study.**

Balancing the potential risks ~~identified in association with~~ **of** retosiban **treatment against** ~~are justified by~~ the anticipated benefits ~~that may be~~ afforded to subjects with preterm labor**,** ~~T~~**t**he overall benefit:risk assessment of retosiban appears ~~favorable~~ **reasonable** for the mother, fetus, and infant. ~~Although, experience in pregnant women is limited, no clinical or preclinical safety issues have been identified that preclude further development.~~

For detailed information on the identified risks and risk-benefit assessment of retosiban, refer to the IB **and IB supplement 1 [GlaxoSmithKline Document Number CM2006/00201/03; GlaxoSmithKline Document Number 2015N228508_00]**.

Section 5., Selection of Study Population and Withdrawal Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GlaxoSmithKline (GSK) IP or other study treatment that may affect subject eligibility is provided in the IB, **IB Supplement 1,** and other pertinent documents **[GlaxoSmithKline Document Number CM2006/00201/03; GlaxoSmithKline Document Number 2015N228508_00]**.

Section 5.1., Inclusion Criteria

5. Current or past tocolytic treatment as follows:
    a. Subjects in whom tocolytic treatment has not been initiated prior to consent are eligible for the study
    b. Transferred or referred subjects for whom parenteral magnesium sulfate treatment has been started before Screening are eligible provided they meet all eligibility criteria
    c. Subjects receiving ~~another~~ **a prohibited** tocolytic ~~not permitted~~ in this study are eligible only if the treatment is stopped before randomization and provided they meet all eligibility criteria
    d. Subjects with a historical failure of a tocolytic treatment in a previous episode of preterm labor during the current pregnancy are eligible provided they meet all eligibility criteria

e.

Section 6.1., Investigational Product and Other Study Treatment

The retosiban infusion will be prepared by an unblinded pharmacist or other qualified professional, using two 5 mL retosiban vials admixed in a 500 mL 0.9% NaCl infusion bag to obtain a concentration of 0.3 mg/mL (150 mg retosiban in 500 mL 0.9% NaCl). The infusion admixture is a clear, colorless solution.

An unblinded pharmacist or other qualified individual will prepare the placebo ~~of~~ **infusion using** 0.9% NaCl **500 mL** matched for the retosiban loading dose and continuous infusion rates, including a dose increase in subjects with an inadequate response **any time** after the first hour of treatment.

Table 1 summarizes the study treatments.

Table 1 Retosiban Investigational Product and Other Study Treatment

Product Name	Study Treatment Retosiban (GSK221149) Solution for Infusion	Study Treatment PTM IV Solution (0.9% NaCl)
Drug product description	Clear, colorless solution for infusion in a 5-mL vial containing 75 mg of retosiban	A placebo-matched glass vial is not provided.
Unit dose strengths/ Dosage levels	Retosiban 15 mg/mL The total dose given over 48 hours should not exceed 300 mg at the 6-mg/hour infusion rate and 582 mg at the 12-mg/hour infusion rate.	0.9% NaCl matched for the retosiban loading dose and continuous infusion rates
Route of administration	IV	IV
Dosing instructions:	The retosiban 6-mg loading dose is administered at an infusion rate of 240 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 20 mL/hour to deliver retosiban at a rate of 6 mg/hour for the remainder of the 48-hour treatment period. ~~An adequate treatment response is defined as a clinically relevant reduction in the frequency of contractions without an increase in cervical dilation.~~ For subjects with an inadequate response **any time** after the first hour of treatment, investigators should administer another 6-mg loading dose by increasing the infusion rate to 240 mL/hour for 5 minutes, after which the infusion rate is set to 40 mL/hour in order to deliver retosiban at a rate of 12 mg/hour. For subjects receiving concomitant treatment with a strong CYP3A4 inhibitor, the retosiban 3-mg loading dose is administered at an infusion rate of 120 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 6.7 mL/hour to deliver retosiban at a rate of 2 mg/hour. For subjects with an inadequate response **any time** after the first hour, an additional 1-mg loading dose is administered by increasing the infusion rate to 40 mL/hour over 5 minutes after which the infusion rate is set to 10 mL/hour to deliver retosiban at 3 mg/hour for the remainder of the 48-hour treatment period. For subjects receiving concomitant treatment with a strong CYP3A4 inducer, the retosiban 8.5-mg loading dose is administered at an infusion rate of 340 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 28 mL/hour to deliver retosiban at a rate of 8.5 mg/hour. For subjects with an inadequate response **any time** after the first hour, an additional 3.5-mg loading dose is administered by increasing the infusion rate to 140 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 40 mL/hour to deliver retosiban at	Intravenous administration of the 0.9% NaCl solution will be matched to the loading dose rate of 240 mL/hour for 5 minutes, after which the infusion rate is set to 20 mL/hour. ~~An adequate treatment response is defined as a clinically relevant reduction in the frequency of contractions without an increase in cervical dilation.~~ For subjects with an inadequate response **any time** after the first hour of treatment, investigators should administer another loading dose by increasing the infusion rate to 240 mL/hour for 5 minutes, after which the infusion rate is set to 40 mL/hour. For subjects receiving concomitant treatment with a strong CYP3A4 inhibitor, the loading dose is administered at an infusion rate of 120 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 6.7 mL/hour. For patients with an inadequate response **any time** after the first hour, an additional loading dose is administered by increasing the infusion rate to 40 mL/hour over 5 minutes, after which the infusion rate is set to 10 mL/hour. For subjects receiving concomitant treatment with a strong CYP3A4 inducer, the loading dose is administered over 5 minutes at an infusion rate of 340 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 28 mL/hour. For patients with an inadequate response **any time** after the first hour, an additional loading dose is administered by increasing the infusion rate to 140 mL/hour for 5 minutes. After 5 minutes, the infusion rate is reduced to 40 mL/hour. See Study Pharmacy Manual for detailed instructions.

Product Name	Study Treatment	
	Retosiban (GSK221149) Solution for Infusion	**PTM IV Solution (0.9% NaCl)**
	a rate of 12 mg/hour. See the Study Pharmacy Manual for detailed instructions.	
Manufacturer/ Source of procurement	GSK	Not applicable – to be sourced locally

CYP3A4 = cytochrome P450 3A4 enzyme; IV = intravenous; GSK = GlaxoSmithKline; NaCl = sodium chloride; PTM = placebo to match.

Section 6.3.1., Inadequate Response

An adequate treatment response is ~~defined as a~~ **based on (1)** clinically relevant reduction **of contraction** frequency **and/or intensity or** ~~without an increase in~~ **(2) no change in the** cervical ~~dilation~~ **examination**. For subjects with an inadequate response **any time** after the first hour of treatment with retosiban or matching placebo, investigators should administer another 6 mg loading dose by increasing the infusion rate to 240 mL/hour for 5 minutes, after which the infusion rate is set to 40 mL/hour in order to deliver retosiban at a rate of 12 mg/hour. Investigators will be required to indicate in the eCRF the reason or reasons for a dose increase. A subject's response should be assessed for at least 1 hour following a dose increase before a decision is made to discontinue randomized treatment ~~due to lack of~~ **an inadequate** response.

Section 6.4., Blinding

The IDMC will review unblinded data periodically ~~as part of~~ **in addition to** 2 formal interim analyses ~~and~~ in accordance with the IDMC charter. Unblinded data will be provided by an independent statistical data analysis committee.

This will be **a** double-blind study and the following will apply:

Section 6.6., Preparation/Handling/Storage/Accountability

The following are the preparation instructions for the retosiban solution for infusion:

- Withdraw 10 mL solution from a 500 mL 0.9% NaCl infusion bag and discard the solution
- Replace discarded solution with 10 mL retosiban 15 mg/mL concentrate solution for infusion from two 5 mL vials to obtain a concentration of 0.3 mg/mL (150 mg retosiban in 500 mL 0.9% NaCl). The reconstituted product is a clear, colorless solution without particles
- Label the IV bag with the **following information**: subject number, **date, protocol number, dosing session number,** investigator's name, ~~dosing session number,~~ **and the statement, "use as directed per pharmacy manual"** (~~as described in the~~ **for details see the** Study Pharmacy Manual).

Once the vial of retosiban solution has been opened, the dilution must be performed immediately. The diluted solution for IV administration should be used within 24 hours after preparation **in order to minimize the risk for microbial growth**. The volume for the infusion bag must be 500 mL to avoid proportional calculations.

The unblinded pharmacist or other qualified individual will prepare the placebo admixture, which will consist of a 500-mL 0.9% NaCl infusion bag, labeled with the **following information:** subject number, **date,** protocol number, ~~infusion rate, and~~ dosing session number**, investigator's name, and the statement, "use as directed per pharmacy manual."** The volume of the 0.9% NaCl infusion bag should 500 mL to match the 0.9% NaCl infusion bag volume used for the retosiban admixture **(for details see the Study Pharmacy Manual)**.

A description of the methods and materials required for preparation of the retosiban solution and the matching placebo are detailed in the Study Pharmacy Manual~~, which will be accompanied by a Quality Agreement~~.

The following considerations must be made with regard to IP preparation, handling, storage, and accountability in this study:

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records)
- Further guidance and information for final disposition of unused study treatment are provided in the ~~SPM~~ **Study Pharmacy Manual**
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, medical monitor, and/or GSK study contact
- A material safety data sheet or equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or will be made available upon request from GSK

Section 6.10., Prior Medications and Nondrug Therapies

Prior medications will be reviewed and the investigator will attempt to obtain a complete history of any medications taken during the pregnancy (including the trimester of exposure, if possible) and during any previous episodes of preterm labor (e.g., magnesium sulfate ~~for neuroprotection~~ or antenatal corticosteroid treatment).

Section 6.11.1.1., Antenatal Corticosteroids

Antenatal corticosteroid ~~for fetal maturation treatment~~ should be administered ~~in accordance institutional guidelines (see Section 4.5.2)~~ **as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone every 12 hours administered intramuscularly, if treatment has not been given within 7 days of study**.

Section 6.11.1.2., Magnesium Sulfate

~~Magnesium sulfate for fetal neuroprotection and/or tocolysis is permitted (see Section 4.5.3).~~ **Investigators have the option to use magnesium sulfate. Magnesium sulfate should be given intravenously using a 4- to 6-g loading dose and 1- to 2-g/hour infusion rate. The total duration of magnesium sulfate administration should not exceed 48 hours.**

Section 6.11.1.4., Antibiotics

~~Antibiotic treatment for GBS is allowed per institutional guidelines.~~ **Intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection will be permitted.**

Section 6.11.2., Prohibited Medications and Nondrug Therapies

Except for IP administered during this study, no additional investigational drugs or investigational devices are permitted for the mother from the time of study entry through completion of the follow-up visit (i.e., the maternal post-delivery assessment) or 30 days after administration of the last dose of IP, whichever is longer. ~~Concomitant use of other tocolytics except for magnesium sulfate is prohibited (see Section 5.1, inclusion criterion 5, for permitted current or past tocolytic treatment at time of Screening).~~

Section 6.11.2.1., Tocolytic Drugs

Concomitant use of calcium-channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), or β-agonists for tocolysis during IP administration is prohibited. Likewise, the use of calcium-channel blockers, NSAIDs, or β-agonists for maintenance tocolysis in subjects who remained undelivered following the Inpatient Treatment Phase is prohibited.

Table 2 Time and Events Table

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase**[1]	**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**
	Day 0	**Day 1**	**Day 2**	**Every week (or early termination/ withdrawal)**	**Information collected via medical records review**	**6 weeks (±2 weeks) after delivery**	**Delivery to 28 days post EDD**
Clinical and Other Assessments							
Written informed consent and medical releases for treatment[2]	X						
Discuss and request consent for participation in the infant follow-up study[3]	X◄	———	———	———	———	———	►X
Inclusion/exclusion criteria confirmation	X						
Baseline characteristics and demographic data	X						
Medical history (including obstetrics history)[4]	X						
~~Urine d~~**D**rug ~~screen~~ and alcohol ~~breath analyzer~~ **screening**[5]	X						
Physical examination (including height and weight)	X						
Cervical ~~dilation based on digital~~ examination[6]	X	X	X	X			
Estimated fetal weight via ultrasound	X						
Determine AFI via ultrasound[7]	X						
Uterine contractions[8]	X						
Schedule post-infusion assessment visit			X				
Investigational Products[9]							
Retosiban or placebo		X	X				

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase[1]**	**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**
	Day 0	**Day 1**	**Day 2**	**Every week (or early termination/ withdrawal)**	**Information collected via medical records review**	**6 weeks (±2 weeks) after delivery**	**Delivery to 28 days post EDD**
Efficacy Assessments							
Date and time of delivery[10]					X		
Mode of delivery[10]					X		
Indication for delivery[10]					X		
Neonatal composite outcomes							X
Neonatal hospital stay							X
Maternal Safety Assessments							
Concomitant medications	X◄	———	———	———	———	►X	
ECG 12-lead[11]	X						
Vital sign measurements (BP, pulse rate, temperature, and oxygen saturation)[12]	X	X	X	X			
AEs, SAEs, and DREs : maternal	X◄	———	———	———	———	►X	
Monitor fluid balance	**X**	**X**	**X**				
Breastfeeding status						X	
Edinburgh Postnatal Depression Scale[13] (maternal)						X	
Local laboratory assessments (LFTs only)[14]	X						
Central laboratory assessments (including hematology, chemistry, and LFTs)[15]	X		X	X[15]			
Physical examination (brief)				X			
Status of postpartum bleeding						X	
Fetal Safety Assessments							
Fetal heart rate monitoring[16]	X	X◄	———	►X	X		
AEs, SAEs, and DREs: fetal	X◄	———	———	———	———	►X	

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase[1]**	**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**
	Day 0	**Day 1**	**Day 2**	**Every week (or early termination/ withdrawal)**	**Information collected via medical records review**	**6 weeks (±2 weeks) after delivery**	**Delivery to 28 days post EDD**
Neonatal Safety Assessments							
AEs, SAEs, and DREs: neonatal					X ◄——— ———► X		
Neonatal Apgar Scores (1 and 5 minutes)[10]					X		
Neonatal growth parameters[10]					X		
Neonatal umbilical cord blood gases[10]					X		
Health Outcome Assessments							
Maternal and neonatal health care resource use[17]					X		X
Pharmacokinetic Assessments							
Maternal PK blood sample[18]		X[18] ◄——► X					
Cord blood sample[19]					X		
Breast milk/colostrum sample[20]					X		
~~Histopathology~~							
~~Placental tissue sample[21]~~					~~X~~		
Genetic and Biomarker Assessments							
Genetic **blood sample for** maternal ~~blood sample~~ **DNA[22][21]**	X						
Biomarker ~~for inflammation (~~maternal~~)~~ **blood sample[21]**	X						
~~Cord blood sample for g~~**G**enetic ~~and biomarker assays~~ **blood sample for cell-free fetal DNA**[23]					X		
Other Assessments							
Fetal fibronectin (optional)[24]	X						
Cervical length via transvaginal ultrasound (optional)[25]	X						
Confirm no other study participation for infant[26]							X

AE = adverse event; AFI = amniotic fluid index; ALT = alanine aminotransferase; BP = blood pressure; DRE = disease-related event; ECG = electrocardiogram; eCRF = electronic case report form; EDD = estimated date of delivery; IP = investigational product; LFT = liver function test; PK = pharmacokinetic; SAE = serious adverse event; ULN = upper limit of normal.

1. Subjects who remain undelivered after 48 hours will return for a face-to-face post-infusion visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase. The subject will then be contacted every week via telephone to determine and record if she has delivered or experienced any subsequent episodes of preterm labor. Note: If the subject is scheduled to visit the clinic for reasons not required by this protocol and/or she happens to be present at the time the telephone assessment is due, this assessment may be completed face-to-face.
2. Prestudy screening information that is collected by the study site may need to come from records that are obtained before the subject has signed the informed consent. The subject will be required to provide written informed consent before any study-specific procedures are performed, and the consent will request permission for use of any information collected prior to its having been signed.
3. During the study, the subject or other legal guardian for the infant (both delivered and undelivered) will be asked to give consent for the infant to participate in a separate long-term infant follow-up study for safety and neurodevelopment. Withdrawal from the study after beginning randomized treatment or discontinuing IP does not preclude involvement in the infant follow-up study.
4. Medical history will be collected at Screening. If a condition with a start date predating Day 0 (Screening) is subsequently discovered, the condition should be recorded in the Medical History eCRF. For obstetrics history, the investigator will make every effort to obtain this information either via computer records, directly from the subject's primary care obstetrician, or via telephone. However, in cases in which these records are not readily available (e.g., off hours, holiday), it is within the investigator's discretion to use gestational age based on the verbal history from the subject with the intent of getting confirmation from the medical records as soon as possible.
5. The urine drug screen will be performed using a point-of-care, qualitative testing device. A point-of-care breath analyzer for alcohol will be used in some countries in addition to the urine drug screen.
6. A cervical examination (including dilation, effacement, and station) will occur at Screening, and an additional cervical examination may be performed before dosing based on investigator discretion. If a predosing cervical examination reveals dilation >4 cm, the subject cannot be dosed. Additional cervical examinations (Day 1, Day 2, and/or at the face-to-face post-infusion assessment visit) will be performed based on investigator discretion.
7. The abdominal ultrasound for determination of the AFI will be performed at Screening for all subjects.
8. Uterine tocography will be performed prior to dosing to confirm the uterine contraction frequency. If the examination reveals a rate that is <4 contractions over a 30-minute interval, the subject cannot be dosed.
9. Antenatal corticosteroid treatment should be administered ~~in accordance with institutional guidelines~~ **using either betamethasone or dexamethasone, if treatment has not been given within 7 days of study enrollment. Investigators have discretion to use a standardized regimen of magnesium sulfate, as well as intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection**. ~~Magnesium sulfate can be administered for fetal neuroprotection in accordance with institutional guidelines. Magnesium sulfate can also be administered as an adjunctive treatment to support antenatal corticosteroid therapy for up to 48 hours.~~
10. Information regarding delivery will be obtained through a review of the hospital and medical records. Growth parameters include neonatal weight, length, and head circumference.
11. A 12-lead ECG will be performed prior to dosing. If the results are interpreted by the investigator to have clinically significant abnormalities, the subject cannot be dosed.
12. Blood pressure, pulse rate, and temperature will be assessed at Screening, once every 4 to 8 hours as part of maternal safety monitoring during the Inpatient Randomized Treatment Phase, and at the post-infusion assessment visit. Oxygen saturation will be assessed by pulse oximetry at Screening and once every 4 to 8 hours during the Inpatient Randomized Treatment Phase; oxygen saturation less than 92% should be recorded as an AE or SAE, as appropriate.
13. Maternal subjects will complete the Edinburgh Postnatal Depression Scale, a self-reported questionnaire, at the maternal follow-up assessment 6 weeks (±2 weeks) after delivery.

14. The LFTs should be ordered from the local laboratory to confirm that ALT is not ≥2 × ULN OR total bilirubin is not >1.5 × ULN (>35% direct bilirubin) before dosing with the IP. An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%. Screening LFT laboratory results do not need to be available for the subject to be randomly assigned to treatment; however, see Section 5.3.3 if ALT or bilirubin is abnormal.
15. Hematology, chemistry, and LFTs will be determined through a central laboratory. The LFT values from the central laboratory should be reviewed for abnormalities (see Section 5.3.3). For subjects who deliver within 24 hours after completion or discontinuation of IP and for subjects who deliver at the investigative center after discharge but before the face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and LFTs should be performed.
16. Prior to dosing, if the fetal heart rate is nonreassuring, the subject cannot be dosed. Fetal heart rate monitoring will be continuous throughout the Inpatient Randomized Treatment Phase. The fetal heart rate will be recorded in the eCRF once every 4 to 8 hours in conjunction with maternal vital signs. If the subject has not delivered at the end of the Inpatient Randomized Treatment Phase, fetal heart rate will be recorded at the face-to-face post-infusion assessment visit. Any fetal heart rate assessment of Category II or III will be reported as an AE of special interest on a specified eCRF (details in Section 7.4.4).
17. Maternal and neonatal health care resource use may include, but is not limited to, neonatal complications requiring intensive or specialized care, neonatal hospital readmission, and neonatal ambulatory surgery.
18. PK samples will be taken at each of the following sampling windows (relative to the start of the infusion on Day 1): 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 54 hours. In addition, a PK sample should be taken at the onset of any maternal or fetal SAE that occurs within 12 hours after completion or discontinuation of IP.
19. In subjects who deliver at an investigative center within 12 hours following completion or discontinuation of the IP, ~~the single~~ **a** cord blood sample will be ~~divided~~ **collected** for PK analysis~~; this is in addition to using the cord blood sample for biomarker and genetic analyses (if additional consent for genetic testing is provided)~~.
20. A breast milk/colostrum sample is only to be collected in women who deliver and produce breast milk within 12 hours after completion or discontinuation of the IP.
21. ~~A placental tissue sample will be collected at delivery in subjects who deliver at an investigative center for both a local and central laboratory pathological examination.~~ **All participating investigational centers will collect a blood sample for maternal DNA in women who provide informed consent for genetic research.**
22. ~~A blood sample for genetic research will only be collected from subjects who provide informed consent.~~ **All participating investigational centers will collect a maternal blood sample for biomarker research.**
23. ~~A single cord blood sample will be collected in subjects who deliver at an investigative center, and the sample will be divided for analyses of biomarkers, genetics (if additional consent for genetic testing is provided), and pharmacokinetics (if delivery is at an investigative center and within 12 hours after completion or discontinuation of the IP).~~ **Only US and Canadian investigational centers will collect a maternal blood sample for cell-free fetal DNA in women who provide informed consent for genetic research.**
24. Fetal fibronectin results will be collected only at those institutions that perform fetal fibronectin testing as routine practice. Fetal fibronectin will not be used to determine study eligibility.
25. Cervical length determined by transvaginal ultrasound will be collected only at those institutions that measure cervical length as routine practice. Cervical length will not be used to determine study eligibility.
26. Obtain confirmation from the subject or the legal guardian for the infant that the infant is not participating in any other study.

Section 7.3.1., Time to Delivery or Treatment Failure

The first of the two co-primary efficacy endpoints is a composite for the time elapsed between the beginning of treatment and delivery or treatment failure, whichever occurs first.

Section 7.3.1.1., Time to Delivery

The time to delivery will be assessed from the start of study treatment administration (time 0) in the Inpatient Randomized Treatment Phase until delivery. ~~Subjects who have not delivered by the end of treatment will return for a face-to-face post infusion visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase. The subject will then be contacted every week via telephone to determine and record if she has delivered.~~ For this efficacy assessment, medical records for the delivery and hospitalization for mother and newborn will be reviewed in order to record the following information:

Section 7.3.1.2., Time to Treatment Failure

Treatment failure will be defined as the administration of any putative tocolytic medication, such as calcium-channel blockers, NSAIDs, or D-agonists. The time to treatment failure will be assessed from the start of study treatment administration (time 0) in the Inpatient Randomized Treatment Phase until a putative tocolytic is administered.

Treatment failure will be considered to have occurred in the following situations:

- **Administration of a tocolytic following IP discontinuation during the Inpatient Randomized Treatment Phase.**
- **Administration of a tocolytic in an undelivered subject for the management of recurrent preterm labor.**
- **Maintenance tocolysis is prohibited (Section 6.11.2.1); however, any subject treated with a tocolytic as maintenance treatment during the Post-infusion Assessment Phase will be considered a treatment failure.**

For this efficacy assessment, the following information will be collected:

- **Date and time of administration of any putative tocolytics**
- **Name and dose of the putative tocolytics**
- **Reason for administration of putative tocolytics**

Operational procedures will be instituted to optimize data collection and reporting consistency in those situations when the subject is administered an alternative tocolytic by her referring primary care obstetrician. Details of these procedures are provided in the SPM.

Section 7.4.1.3., Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 7.4.1.4) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.3.1.2). **For newborns participating in the infant follow-up study, unresolved SAEs and AEs of special interest will be followed to stabilization or resolution in the long term follow-up study.** Further information on follow-up procedures is given in Appendix 3.

Section 7.4.1.7.2., Disease-Related Neonatal Events (Occurring in Infants Born Prior to 37 Completed Weeks)

- Gastrointestinal
  - Gastroesophageal reflux
  - Aspiration pneumonia
- Hematologic
  - Anemia ~~(severe)~~
- Vision
  - Retinopathy of prematurity (all stages)

However, if one or all of the following conditions apply, then the event should be reported as an AE/SAE as indicated in Appendix 3 (Section 12.3.4):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject,
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the IP, or
- An event defined as a disease-related neonatal event ~~is reported~~ **occurs** in an infant born ≥37 completed weeks

Section 7.4.4., Fetal Heart Rate Monitoring

Fetal heart rate will be monitored continuously from Screening until completion of the 48-hour Inpatient Randomized Treatment Phase. Subjects will be allowed breaks of up to 1 hour if fetal heart rate monitoring up to that point has been reassuring. Fetal heart rate should be recorded in the eCRF once every 4 to 8 hours at approximately the same time that maternal vital sign measurements are collected (Section 7.4.3). Fetal heart rate also will be recorded at the face-to-face post infusion assessment visit if the subject remains undelivered. During the Delivery Phase, fetal heart rate monitoring information will be collected from review of medical records. Any fetal heart rate assessment of Category II or III according to the following criteria and based on ACOG guidelines [ACOG Practice Bulletin No. 106, 2009] will be reported as an AE of special interest on a specified eCRF **in addition to the corresponding AE or SAE eCRF**:

Section 7.4.6., Clinical Safety Laboratory Assessments

With the exception of the above, all protocol-required laboratory assessments must be performed by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and protocol Time and Events Table. Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

The volume of blood required for hematology, chemistry, and liver function tests, as specified in the Time and Events Table (Table 2), is approximately 20 mL.

Section 7.4.8., Fluid Management

Care should be taken to assess for fluid overload by monitoring the total fluid balance from the Screening Phase through Inpatient Randomized Treatment Phase and assessing for signs and symptoms of fluid overload. Details regarding this assessment are provided in the SPM.

Section 7.6.1., Sampling

Maternal blood samples for the quantification of retosiban in plasma will be taken at the following sampling windows (relative to the start of the infusion on Day 1): 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 54 hours, the last point being after the end of the infusion. Samples may be taken at any time within these windows, but the exact time of the sample should be recorded in the eCRF. **The volume of blood required for PK sampling, as specified in the Time and Events Table (Table 2), is approximately 8 mL.**

In addition, a blood sample should be taken at the onset of any maternal or fetal SAE that occurs within 12 hours after completion or discontinuation of IP.

Section 7.6.2., Umbilical Cord Blood

For those subjects who deliver at the investigative center within 12 hours following completion or discontinuation of IP, ~~the~~ **a** single **3 mL** cord blood sample **will be** collected ~~and divided for potential biomarker assays (Section 7.10) and genetic research (Section 7.11) should also be divided~~ for a PK analysis of fetal drug exposure. The date and time the sample was collected should be noted in the eCRF. If the investigator deems that umbilical cord blood is needed to provide care for the infant (e.g., neonatal transfusion or laboratory testing), collection for clinical use will be prioritized over **PK** sampling for the study.

~~7.7. Histopathology~~

~~A placental tissue sample will be collected for pathologic examination when delivery occurs at an investigational center. Guidelines have been developed to ensure a consistent~~

~~evaluation of the placenta, membranes, and umbilical cord across the multiple centers participating in this study. Each investigator should review these guidelines and procedures, which are provided in the SPM. Gross examination of the intact placenta, umbilical cord, and membranes should be performed by the hospital pathology department with gross findings reported in a standardized manner. In addition, the hospital pathology department will need to prepare tissue sections for histologic examination of placenta, membranes, and umbilical cord by a central pathology laboratory.~~

Section 7.9., Biomarkers

~~Biomarkers may be determined from a maternal blood sample collected at Screening and from the single cord blood sample collected during the Delivery Phase (only for those subjects who deliver at the investigative center).~~ **A** ~~B~~**b**iomarkers ~~**is a molecule associated specifically with a disease or condition such that it allows for the diagnosis, risk identification, or optimization of treatment. A 3.5-mL maternal blood sample for biomarker research will be collected at Screening**~~. The samples will be stored and may be analyzed for future exploratory research.

Section 7.10., Genetics

Pharmacogenetics is the study of how drug response varies in individuals due to genetic differences. Genetic differences also may contribute to preterm labor risk and progression. Two ~~At Screening (Day 0), a maternal~~ blood sample**s** will be collected **at Screening in** ~~from~~ subjects who ~~sign the optional~~ **provide** informed consent for genetic research**: a 6-mL sample for maternal DNA (at all participating investigational centers) and a 8.5-mL sample for cell-free fetal DNA (at US and Canadian investigational centers only).** ~~In addition, for those subjects who deliver at the investigative center, the single cord blood sample will be divided and used for genetic research.~~

Information regarding genetic research is included in Appendix 5.

Section 9.1., Hypotheses

The co-primary endpoints ~~are neonatal composite outcome and the~~ **assess** prolongation of pregnancy ~~as measured by~~ **using** time to delivery ~~(days)~~ **or treatment failure, whichever comes first, and neonatal outcomes using a morbidity and mortality composite**. The following are the null (H0) and alternative (H1) hypotheses for the **co**-primary endpoints in this study:

Time to delivery **or treatment failure**:

- H_0: prolongation of pregnancy as measured by time to delivery **or treatment failure** of women is equal between retosiban versus placebo
- H_1: prolongation of pregnancy as measured by time to delivery **or treatment failure** of women is unequal between retosiban versus placebo

Neonatal composite outcome:

- H_0: Incidence of neonatal composite outcome is equal between retosiban versus placebo
- H_1: Incidence of neonatal composite outcome is unequal between retosiban versus placebo

The hypotheses will be tested using a sequential testing procedure to control the overall type I error rate at the 5% level. Additionally, an O'Brian-Fleming alpha spending function will be employed to control the type I error for the planned interim analyses. ~~For the planned sample size of~~ **The O'Brien-Fleming boundaries to be used at the second interim analysis and final analysis will be based on the actual information fraction, which will be the ratio of the actual sample size at the second interim analysis and the re-estimated final sample size (see Section 9.2.3). For example, if the actual sample size at the second interim analysis is** 400 women/newborn pairs **and the re-estimated sample size remains** at 800 women/newborn pairs ~~at the end of the study~~, the hypotheses ~~will~~ **would** be tested at the 0.52% and 4.8% levels, respectively. Thus, at the second interim analysis, the hypothesis for time to delivery **or treatment failure** ~~will~~ **would** be tested first at the 0.52% level, and the hypothesis for neonatal outcome ~~will~~ **would** then be tested at the 0.52% level only if the null hypothesis for the time to delivery **or treatment failure** is rejected. Similarly, at the final analysis, the hypothesis for time to delivery **or treatment failure** ~~will~~ **would** be tested first at the 4.8% level, and the hypothesis for neonatal outcome ~~will~~ **would** then be tested at the 4.8% level only if the null hypothesis for the time to delivery **or treatment failure** is rejected. No further adjustments to the type I error rate are planned for the co-primary endpoints. Details of the methodologies to control the type I error will be included in the IDMC and study reporting and analysis plans (RAPs).

Section 9.2.1, Sample Size Assumptions

A total of 900 women (450 women in each group) will be recruited into the study and randomly assigned to ensure that 800 (400 women/newborns in each group) have recorded birth data, which provides 86% statistical power to detect a relative risk of 68% between retosiban and placebo in neonatal outcomes in the proposed adaptive design with futility stopping, success stopping, and sample size re-estimation. Calculations assume a placebo incidence rate of 34%.

Additionally, the sample size of ~~900~~ **800** women (approximately ~~450~~ **400** women/newborn pairs per group) provides at least 90% statistical power to detect a difference of ~~9~~**5**.5 days in the **co-primary endpoint,** time to delivery **or treatment failure, and the key secondary endpoint, time to delivery,** between retosiban and placebo.

The sample size calculations are based on a 2-sided testing procedure with a type I error rate of 4.8% **(e.g., O'Brien-Fleming boundary based on planned information fraction)** and an approximate 10% dropout rate. Calculations are based on simulations and assume that the percentage of women enrolled into each of the GA strata $24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$, and $31^{0/7}$ to $33^{6/7}$ will be 7%, 13%, 27%, and 53% (1:2:4:8 ratio), respectively, and approximately 55% of women in the placebo arm will

deliver within the 3 weeks of randomization. The details of model assumption and simulation are on file with GSK.

Section 9.2.3., Sample Size Re-Estimation or Adjustment

The sample size may be adjusted at the second interim analysis. The sample size re estimation will be conducted in a manner to maintain the study blind **and will be carried out prior to the formal statistical interim analysis described in Section 9.3.4**. The re-estimation sample size will be based only on the blinded observed overall pooled rate of neonatal composite and will be conducted by the blinded team. The sample size may be increased by a minimum of 50 women/newborn pairs up to a maximum sample size of 1200 women/newborn pairs. **The re-estimated sample size in conjunction with the actual sample size for the second interim analysis will be used to determine the O'Brien Fleming boundaries to be used in the interim and final analyses.**

The details of the sample size re-estimation methods **and determination of the corresponding O'Brien-Fleming boundaries** will be provided in the RAP.

Section 9.3.1.3., Maternal Per-Protocol Population

This Maternal Per-Protocol Population is defined as all subjects in the Maternal ITT Population excluding those who are major protocol violators. Subjects will be analyzed according to their actual treatment in case this differs from their randomly assigned treatment. This will include exclusions for use of prohibited concomitant medications and **treatment** failure to meet inclusion criteria specified by the protocol.

Section 9.3.2.3., Neonatal Per-Protocol Population

The Neonatal Per-Protocol Population is defined as all subjects in the Neonatal ITT Population excluding those with~~out~~ major protocol violations.

Section 9.3.3.1., Primary Comparisons of Interest

The primary comparison of interest is retosiban versus placebo for the co-primary endpoints: time to delivery **or treatment failure** and neonatal composite endpoint. The comparison will be based on the ITT Population, and a sequential testing procedure will be used to control the overall type I error rate at 5% level with time to delivery **or treatment failure** being tested first.

Section 9.3.3.2., Other Comparisons of Interest

The comparison of retosiban versus placebo will also be performed for key secondary endpoints: **time to delivery,** proportion of preterm births ($<37^{0/7}$ weeks' gestation), proportion of births $\geq 37^{0/7}$ weeks' gestation, and neonatal length of hospital stay. Other comparisons of exploratory endpoints between retosiban and placebo will be discussed in the RAP.

Section 9.3.3.3., Subgroup Analysis

Additionally, comparisons of retosiban versus placebo for co-primary and key secondary endpoints may also be performed for the following subgroups:

- GA strata $24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$, or $31^{0/7}$ to $33^{6/7}$
- Established progesterone use (yes or no)
- **Magnesium sulfate use**
- **Tocolytic use following IP discontinuation**

Other potential subgroup comparisons will be described in the RAP.

Section 9.3.4., Interim Analyses

Two interim analyses are planned~~, at which time the co-primary endpoints will be statistically analyzed~~. The first interim analysis will occur after approximately 150 women/newborn pairs complete all assessments. The primary objective of the first interim analysis is to determine if the study should be terminated for lack of efficacy (futility) based on prespecified criteria. The decision will be based primarily on the analysis of the ~~co-primary~~ **key secondary** endpoint **of** time to delivery; however, all available safety and efficacy data will be reviewed.

Time to delivery will be analyzed ~~as~~ **similarly to analyses** described ~~for the primary efficacy analyses~~ **in Section 9.4.1.1**. An estimate of the difference in time to delivery between the retosiban and placebo groups will be computed. Additionally, the conditional power of rejecting the null hypothesis at the end of the study based on the observed difference will be computed.

The second interim analysis will occur after approximately 400 women/newborn pairs complete all assessments. The primary objectives of the second interim analysis are to determine if the study should be terminated for either lack of efficacy (futility) or for greater than expected efficacy (success). The decision to terminate for futility will be based on prespecified criteria**, the key secondary endpoint of time to delivery, and the co primary endpoint of neonatal composite**. The decision to stop for success will be based on the sequential testing of the null hypotheses for co-primary endpoints (time to delivery **or treatment failure** and then neonatal composite) at the ~~0.52% significance level~~ **determined O'Brian-Fleming boundary** (the adjusted alpha level ~~will be~~ based on an O'Brian-Fleming alpha spending function and the ~~planned~~ **actual** sample size ~~of 400 women/newborn pairs~~ at the second interim **analysis** ~~and 800 women/newborn pairs at the end of the study~~ **and re-estimated sample size** at the end of the study**, see Section 9.2.3)**. Decisions will be based on ~~both co-primary endpoints, time to delivery and neonatal composite~~ **prespecified criteria**, although all available safety and efficacy data will be reviewed.

Time to delivery **or treatment failure and** ~~will be analyzed similar to the first interim analysis with the addition of calculation of the p-value. T~~**t**he neonatal composite will be analyzed as described in Section 9.4.1.1. Point estimate and associated p-value for **both the difference in time to delivery or treatment failure and** the odds ratio of a neonatal composite occurring between retosiban and placebo will be computed. Additionally, the

conditional power of rejecting the null hypothesis at the end of the study based on the observed odds ratio **of the neonatal composite** will be computed.

Section 9.4.1.1., Primary Analyses

The primary objective of the statistical analysis will be to test the null hypothesis in the ITT Population that there is no difference between retosiban and placebo versus the alternative hypothesis that there is a difference between the 2 co-primary endpoints. **The hypotheses tests will be assessed and confidence intervals constructed using the adjusted alpha level determined by the O'Brien-Fleming boundaries.**

The primary analysis of time to delivery **or treatment failure** will utilize a finite mixture model [McLachlan, 2000] with 2 components, 1 for those women delivering imminently and the other for the women delivering at term. The exact weight of each component will be determined by the observations from these component and model concomitant variables, including treatment, established progesterone use, and GA at randomization. Within each component, the expected time to delivery **or treatment failure** will be modeled as a function of treatment as fixed effect and GA at randomization and established progesterone use (yes or no) as covariates. The model parameters will be estimated using expectation maximization algorithm. Point estimates, associated 100(1 α)% confidence intervals (CIs), and p values for the overall average difference in time to delivery **or treatment failure** between retosiban and placebo will then be derived using a weighted average of model parameter estimates and variance from each subpopulation of the mixture model.

Section 9.4.1.2.1., Key Secondary Analyses

The key secondary analysis for this study includes **time to delivery**, the proportion of births prior to $37^{0/7}$ weeks' gestation, proportion of births at term ($37^{0/7}$ to $41^{6/7}$ weeks' gestation), and length of neonatal hospital stay. To preserve the overall type I error rate, the key secondary analysis will be performed if and only if the null hypothesis of the primary endpoint is rejected. In addition, a stepwise Holm's test will be used to adjust for multiplicity of the key secondary endpoints such that the type I error rate will be maintained at 5%. **The endpoint of time to delivery will be analyzed as described in Section 9.4.1.1.**

Section 9.4.3., Health Outcomes Analyses

To further describe the health outcomes of retosiban, the following subgroups may be explored:

- GA of pregnancy at randomization
- Established progesterone use
- **Magnesium sulfate use**
- **Tocolytic use following IP discontinuation**
- Region/sites

Section 11., References

American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Practice Bulletin No. 106. Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol. 2009;114(1):192 202.

~~American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Committee Opinion 455. Magnesium sulfate before anticipated preterm birth for neuroprotection. Obstet Gynecol. 2010;115:669-71.~~

~~American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Committee Opinion 475. Antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol. 2011;117(2 Pt 1):422-4.~~

American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Practice Bulletin No. 127. Management of preterm labor. Obstet Gynecol. 2012;119(6):1308-17.

~~American College of Obstetricians and Gynecologists on Obstetric Practice Society for Maternal-Fetal Medicine. ACOG Committee Opinion No. 573: Magnesium sulfate use in obstetrics. Obstet Gynecol. 2013;122(3):727-8.~~

~~Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel. Antenatal magnesium sulphate prior to preterm birth for neuroprotection of the fetus, infant and child: national clinical practice guidelines. Adelaide: University of Adelaide; 2010. Available from: http://www.adelaide.edu.au/arch/MagnesiumSulphate2010.pdf (Accessed 05 Nov 2014).~~

Cregan MD, De Mello TR, Kershaw D, McDougall K, Hartmann PE. Initiation of lactation in women after preterm delivery. Acta Obstet Gynecol Scand. 2002;81(9):870 7.

~~Di Renzo GC, Al Saleh E, Mattei A, Koutras I, Clerici G. Use of tocolytics: what is the benefit of gaining 48 hours for the fetus? BJOG. 2006;113(Suppl 3):72-7.~~

Fuchs AR, Fuchs F, Husslein P, Soloff MS, Fernstrom MJ. Oxytocin receptors and human parturition: a dual role for oxytocin in the initiation of labor. Science. 1982;215(4538):1396–8.

GlaxoSmithKline Document Number CM2006/00201/03. Investigator's brochure. APR 2014.

GlaxoSmithKline Document Number 2015N228508_00. Investigator's brochure supplement 1. FEB-2015.

Meis PJ, Goldenberg RL, Mercer BM, et al. The preterm prediction study: risk factors for indicated preterm births. Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development. Am J Obstet Gynecol. 1998;178(3):562-7.

~~Mercer BM, Merlino AA; Society for Maternal-Fetal Medicine. Magnesium sulfate for preterm labor and preterm birth. Obstet Gynecol. 2009;114(3):650-68.~~

Royal College of Obstetricians and Gynaecologists (RCOG) Green top Guideline No. 1B. Tocolytic for women in preterm labour. February 2011a. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg1b/ (Accessed 05 Nov 2014).

~~Royal College of Obstetricians and Gynaecologists (RCOG) Scientific Impact Paper No. 29. Magnesium sulphate to prevent cerebral palsy following preterm birth. August 2011b.~~

Simhan HN, Caritis SN. Prevention of preterm delivery. N Engl J Med. 2007;357(5):477 87.

~~Society of Obstetricians and Gynaecologists of Canada (SOGC) Clinical Practice Guideline 258. Magnesium sulphate for fetal neuroprotection. J Obstet Gynaecol Can. 2011;33(5):516 29.~~

Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010;126(3);443-56.

Stones RW, Paterson CM, Saunders NJ. Risk factors for major obstetric haemorrhage. Eur J Obstet Gynecol Reprod Biol. 1993;48(1):15-8.

Tucker JM, Goldenberg RL, Davis RO, Copper RL, Winkler CL, Hauth JC. Etiologies of preterm birth in an indigent population: is prevention a logical expectation? Obstet Gynecol. 1991;77(3):343-7.

Section 12.1., Appendix 1: Abbreviations and Trademarks

Abbreviations

~~GBS~~	~~group B streptococcal~~
NSAID	**nonsteroidal anti-inflammatory drug**
~~SOGC~~	~~Society of Obstetricians and Gynaecologists of Canada~~

Section 12.3.5., Evaluating AEs and SAEs

Follow-up of AEs and SAEs:
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK/PPD to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK/PPD with a copy of any postmortem findings, including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE **or AE of special interest** data to GSK/PPD within the designated reporting time frames.

Section 12.5., Appendix 5: Genetic Research

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no a priori hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- ~~A~~ **Two** blood sample**s** will be taken for DNA extraction~~. A blood sample is :~~ **one for maternal DNA (at all participating investigational centers) and one for cell-free fetal DNA (at US and Canadian investigational centers only). These samples will be** collected at the screening visit, after the subject has provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample**(s)** are described in the laboratory manual. The DNA from the ~~blood~~ sample**(s)** may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample**(s)**, then the sample**(s)** may be destroyed. The ~~blood sample is~~ **genetic samples are** collected on a single occasion unless a duplicate sample is required due to an inability to use the original sample**(s)**.

- ~~For those subjects who deliver at the investigative center, a cord blood sample will be collected for genetic research.~~

The genetic sample(s) is labeled (or "coded") with the same study-specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Section 12.7., Appendix 7: Country-Specific Requirements

~~No country-specific requirements exist.~~

At US and Canadian investigational centers only:

One maternal blood sample will be taken for DNA extraction to provide cell-free fetal DNA. This sample will be collected at the screening visit, after the subject has provided informed consent for genetic research (see Section 7.10 and Appendix 5).

Protocol Amendment Number 02

Protocol Amendment Number 02 is applicable to all clinical study centers participating in this study. Protocol changes specified in Amendment Number 02 are summarized as follows:

- Revised the guidance for administration of antenatal corticosteroids to read as follows: If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours. A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least 7 days prior to study enrollment.
- Clarified in the Time and Events Table (footnote 15) that hematology, chemistry, and liver function tests will only be determined through a central laboratory at the screening, Day 2, and the face-to-face post-infusion assessment visits.
- Incorporated other administrative changes. The rationale for these changes is to ensure a clear and complete protocol for use at the investigational centers.

Specific Changes in the Text

Synopsis, Overall Design:

- **If not previously administered,** antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours~~, if treatment has not been given within~~ **A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least** 7 days ~~of~~ **prior to** study enrollment.

Section 4.1, Overall Design

If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours~~, if treatment has not been given within~~ **A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least** 7 days ~~of~~ **prior to** study enrollment.

Section 4.2, Treatment Arms and Duration

Figure 2, Study Design

1. Stratification (1:1) to retosiban or matched placebo based on established progesterone therapy at Screening (subjects on established progesterone therapy versus subjects not on established progesterone therapy) and gestational age ($24^{0/7}$ to $25^{6/7}$; $26^{0/7}$ to $27^{6/7}$; $28^{0/7}$ to $30^{6/7}$; $31^{0/7}$ to $33^{6/7}$).
2. **If not previously administered,** antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours**.** ~~, if treatment has not been given within~~ **A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least** 7 days ~~of~~ **prior to** study enrollment.
3. Subjects who have not delivered after 48 hours will return for a face-to-face post-infusion visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) after the Inpatient Randomized Treatment Phase. The subject will then be contacted every week via telephone to determine and record if she has delivered or if she has experienced any subsequent episodes of preterm labor. Retreatment with the investigational product (retosiban or placebo) is not allowed.

An adequate response is based on (1) a clinically relevant reduction of contraction frequency and/or intensity or (2) no change in the cervical examination. Subjects with an inadequate response any time after the first hour of treatment will be administered another 6 mg retosiban or matched placebo loading dose and the retosiban or matched placebo infusion rate will **be** increased to 12 mg/hour for the remainder of the 48 hour treatment period. A subject's response should be assessed for at least 1 hour following a dose increase before a decision is made to discontinue randomized treatment due to lack of response. Investigators will be required to indicate in the electronic case report form (eCRF) the reason or reasons for a dose increase.

Section 6.11.1.1, Antenatal Corticosteroids

If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours**.** ~~, if treatment has not been given within~~ **A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least** 7 days ~~of~~ **prior to** study enrollment.

Section 7, Study Assessments and Procedures

Table 2, Time and Events Table

8. Uterine tocography will be performed prior to dosing to confirm the uterine contraction frequency. If the examination reveals a rate that is <4 contractions over a 30-minute interval, the subject cannot be dosed.
9. If not previously administered, antenatal corticosteroid treatment should be administered ~~using~~ **as** either **(1) two 12-mg doses of** betamethasone **given intramuscularly 24 hours apart** or **(2) four 6-mg doses of** dexamethasone **administered intramuscularly every 12 hours**~~, if treatment has not been given within~~ **A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least** 7 days ~~of~~ **prior to** study enrollment. Investigators have discretion to use a standardized regimen of magnesium sulfate, as well as intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection.
10. Information regarding delivery will be obtained through a review of the hospital and medical records. Growth parameters include neonatal weight, length, and head circumference.

…

15. Hematology, chemistry, and LFTs will be determined through a central laboratory **at the screening, Day 2, and the face-to-face post-infusion assessment visits**. The LFT values from the central laboratory should be reviewed for abnormalities (see Section 5.3.3). For subjects who deliver within 24 hours after completion or discontinuation of IP and for subjects who deliver at the investigative center after discharge but before the face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and LFTs should be performed.

Protocol Amendment Number 03 – Italy Sites Only

The following changes are reflected in the Country-Specific Protocol Amendment for Italy:

- Amend inclusion criteria 1 and 2 to specify that subjects must be at least 18 years of age to participate in Study 200719. Text was revised throughout to reflect the change in the subject age criterion.
- Revise text throughout to indicate that subjects recruited into Study 200719 in Italy must not be dosed with the investigational product until the results of their chemical parameters have been reviewed by the Investigator and no indicators of altered liver function (AST and ALT values and bilirubinemia) are apparent. This check for altered liver function must be carried out before the study drug is administered, i.e., before initiating randomized treatment.

The specific text changes for this country-specific amendment are outlined under Amendment 04.

Protocol Amendment Number 04

Protocol Amendment Number 04 is applicable to all clinical study centers participating in this study. Protocol changes specified in Amendment Number 04 are summarized as follows:

- Added the supportive other secondary endpoints for "the proportion of women experiencing subsequent episodes of preterm labor." This was added to help understand the natural history of pregnancy following treatment with retosiban and to compare with subsequent use of putative tocolytics.
- Clarified the assessments that should be performed at the 1-week face-to-face post-infusion visit and at the weekly telephone calls during the Post-Infusion Assessment Phase. Previously, the face-to-face post-infusion visit and weekly telephone calls were presented together on the Time and Events Table, which resulted in confusion at the sites, as not all assessments indicated in the table are performed during the weekly telephone calls. Additionally, the assessments performed when a subject withdraws from the study were clarified.
- Clarified the concomitant medications that are considered putative tocolytics and added exceptions for putative tocolytic drug use with regard to the definition of treatment failure. Putative tocolytic medications may have dual indications, such as in the treatment of hypertension, respiratory conditions, or chronic medical conditions, for example rheumatoid arthritis. Therefore, specific exceptions for the use of putative tocolytic drugs were added, and the definition of treatment failure was revised to note the exceptions in putative tocolytic drug use.
- Clarified the language for determining gestational age at screening.
- Added that manual palpations may be used for determining contraction frequency in situations where technical difficulties may prohibit accurate measurement.
- Clarified the criteria for confirming sufficient dilation and effacement at Screening.
- Clarified that withdrawal from the study will mean that no additional visits can occur or procedures performed after the subject withdraws from study.
- Included a definition of inadequate response. Although previously the protocol clearly defined adequate response, a clear definition for inadequate response was not included. For maximum understanding of both terms, a definition of inadequate response was added.
- Added a section that outlined the procedures that should be followed for managing dose interruptions. Previously, instructions for dose interruptions were only included in the Study Procedures Manual (SPM), but to ensure sites follow the correct procedures, this information was added to the protocol.
- Added that subject use of a pessary is allowed if use began before the current episode of preterm labor; otherwise, use of a pessary is prohibited. This text, which is included in the SPM, was added to ensure sites were aware of the permitted and prohibited use of a pessary.

- Revised the previous requirements for continuous fetal heart rate monitoring to electronic fetal monitoring for a minimum of 6 hours from the start of the infusion or from the start of a dose increase as long as the fetal heart rate pattern is consistently reassuring throughout the required minimum 6-hour duration of monitoring and the contraction frequency is ≤2 in a 30-minute window within the last hour of monitoring. The previous fetal monitoring requirement was for continuous fetal heart rate monitoring from Screening until completion of the 48-hour Inpatient Randomization Treatment Phase, which proved to be an impediment to subject recruitment.
- Clarified that confirmation of uterine contraction eligibility criterion must occur within 60 minutes before IP dosing. The protocol previously had not included that the 60-minute duration was relative to IP dosing.
- Added respiratory rate to the vital sign measures assessed during the study, and, for consistency with the SPM, clarified the frequency that vital sign and oxygen saturation measurements are assessed relative to dosing.
- Clarified that if a subject does not deliver at the investigative center, central laboratory assessments for hematology, chemistry, and LFTs should be performed at the investigative center within 1 week (acceptable range: 3 to 14 days) after completion of the study drug infusion.
- Revised the visit window for the administration of the Edinburgh Postnatal Depression Scale (EPDS) from ±2 weeks to ±6 weeks, as the 2-week window resulted in protocol deviations and it was determined that it was clinically acceptable to use data for the EPDS up to 12 weeks after delivery.
- Clarified that a maternal blood sample for PK analyses may need to be collected at the same time as the cord blood sample if the sample time does not already coincide with a PK sampling window (i.e., 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 54 hours after the start of the study drug infusion on Day 1).
- Revised the assessment requirement for the first interim analysis. For the first interim analysis, the key secondary endpoint, time to delivery, will be used to determine if the study should be terminated for lack of efficacy (futility) and the analysis will occur when approximately 150 subjects complete delivery; therefore, the protocol was updated to reflect this change.
- Clarified that the second interim analysis to specifically state that this analysis will occur when approximately 400 women/newborn pairs are followed up to 28 days post EDD.
- Added as an appendix guidelines for reporting maternal, fetal, and neonatal adverse events of special interest, which is also provided in the SPM. This was added to provide sites ready access to these detailed guidelines.
- Clarified that the intensity categories for AEs and serious AEs can be found in the SPM. This was changed to provide greater and more granular guidance for the study sites when assessing severity.
- Incorporated the changes detailed in the country-specific amendment for sites in Italy (dated 19 Apr 2016)

- Incorporated other administrative changes. The rationale for these changes is to ensure a clear and complete protocol for use at the investigational centers.

Specific Changes in the Text

Title page:

Authors (GSK): PPD [redacted]

Synopsis, Type and Number of Subjects:

The study population is women aged 12 to 45 years with an uncomplicated singleton pregnancy in preterm labor with intact membranes between $24^{0/7}$ and $33^{6/7}$ weeks' gestation. Approximately 900 women (450 per treatment group) will be randomly assigned to ensure that approximately 800 women/newborns have recorded birth data (assumes approximately 10% missing data).

Italian Subjects: In Italy, the age restriction for study enrollment is 18 to 45 years.

Synopsis, Analysis:

Two interim analyses are planned. The first interim analysis will occur after approximately 150 ~~women/newborn pairs~~ **subjects have** complete**d delivery and have time-to-delivery results available** ~~all assessments~~. The second interim analysis will occur after approximately 400 women/newborn pairs **are followed up to 28 days post EDD** ~~complete all assessments~~.

Section 2.1, Study Rationale

The incidence of birth prior to 37 weeks' gestation in the retosiban group was 18.7% compared with 47.2% in the placebo group (see the investigator's brochure [IB] Section 5.3.2.2.2 [GlaxoSmithKline Document Number CM2006/00201/~~03~~**05**]).

A summary of the complete results for Study OTA105256 is included in the IB (Section 5.3.2.1 [GlaxoSmithKline Document Number CM2006/00201/~~03~~**05**]).

Section 3., Objectives and Endpoints

	Supportive Other Secondary
	• Proportion of births prior to $32^{0/7}$ weeks' gestation • Proportion of births prior to $28^{0/7}$ weeks' gestation • Proportion of births ≤7 days • Proportion of births ≤48 hours • Proportion of births ≤24 hours • Proportion of neonates with any of the co-primary composite neonatal morbidity and mortality, excluding RDS • Proportion of neonates with each individual component of the composite neonatal morbidity and mortality endpoints • Neonatal admission to a specialized care unit and length of stay • Newborn hospital readmission and length of stay • Ambulatory surgery • Time to treatment failure • Proportion of women receiving any putative tocolytic • **Proportion of women experiencing subsequent episodes of preterm labor**

Section 4.2., Treatment Arms and Duration

For those subjects who deliver at the investigative center within 12 hours of IP (retosiban or placebo) completion or discontinuation, a cord blood sample will be collected for pharmacokinetic (PK) analysis**, and, if required, a corresponding maternal blood sample will be collected for PK analysis (see Section 7.6.1)**. Likewise, a breast milk/colostrum sample will be collected for PK analysis in women who deliver at the investigative center and produce breast milk within 12 hours after IP completion or discontinuation.

During the Maternal Post Delivery Assessment Phase, the subject will be contacted by telephone within 6 weeks ~~(±2 weeks)~~ of delivery for a post-delivery assessment, including an assessment of AEs **(±2 weeks)**, status of breastfeeding **(±2 weeks)**, and completion of the EPDS **(±6 weeks)**.

Two interim analyses are planned. The first interim analysis will occur after approximately 150 ~~women/newborn pairs~~ **subjects have** complete**d delivery and have time-to-delivery results available** ~~all assessments~~. The second interim analysis will

occur after approximately 400 women/newborn pairs **are followed up to 28 days post EDD** ~~complete all assessments~~.

Section 4.3, Type and Number of Subjects:

The study population is women aged 12 to 45 years with an uncomplicated singleton pregnancy in preterm labor with intact membranes between $24^{0/7}$ and $33^{6/7}$ weeks' gestation. Approximately 900 women (450 per treatment group) will be randomly assigned to ensure that approximately 800 women/newborns have recorded birth data (assumes ~10% missing data).

Italian Subjects: In Italy, the age restriction for study enrollment is 18 to 45 years.

Section 4.4., Design Justification

To fulfill regulatory requirements to study pediatric subjects, pregnant adolescents aged 12 to 17 years are allowed to participate in this study**, with the exception of sites in Italy, where pregnant adolescents are not eligible to enroll in the study (see Section 5.1)**. . . .

Section 4.5.1, Retosiban

These exposures are significantly less than those studied in the Phase I program, where retosiban doses were well tolerated [GlaxoSmithKline Document Number CM2006/00201/~~03~~**05**]).

Section 4.6., Benefit:Risk Assessment

Summaries of findings from both clinical and nonclinical studies conducted with GSK221149 can be found in the IB. ~~The following section~~ **Table 1 and Table 2** outline~~s~~ the risk assessment and mitigation strategy for this protocol:

Section 4.6.1., Risk Assessment

Table 1 Potential Risks of Clinical Significance

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Fetal exposure through placental transfer	**Retosiban is a substrate of P-gp and BCRP transporters, which are thought to play a role in keeping xenobiotics out of the CNS and out of the fetal blood.** **The** ~~P~~**p**reclinical data indicate very minimal, if any, maternal CNS penetration or placental transfer of retosiban as supported by ~~the following~~: • In pregnant monkeys**,** there was no detectable retosiban in the cord blood when mothers were dosed up to 100 mg/kg (~~approximately~~ **~**7**-fold** ~~times the~~ human exposure). However, approximately 4% of circulating drug was detected in the cord blood when mothers were dosed at 300 mg/kg (~~approximately~~ **~**24-fold ~~the~~ human exposure). ~~Retosiban is a substrate of P-gp and breast cancer resistant protein transporters, which are thought to play a role in keeping xenobiotics out of the CNS and out of the fetal blood, thereby limiting fetal exposure to retosiban.~~ • In reproductive toxicology studies in **monkeys, where retosiban was given to** pregnant monkeys, there were no adverse mother ~~and~~ **or** infant behavioral**,** ~~or~~ locomotor effects observed that were suggestive of CNS toxicity. • In rodent neurobehavioral safety studies, there were no adverse clinical signs observed at doses up to 1000 mg/kg. **Adverse events and serious AEs reported in retosiban**	~~Analysis of m~~**M**aternal blood and cord blood samples will be **analyzed** ~~performed to test~~ for levels of retosiban in women who deliver at an investigative center within 12 hours of the completion or discontinuation of **the** study ~~treatment~~ infusion ~~in this study.~~ ~~Surveillance for signals indicating adverse fetal or neonatal effects with in utero exposure to retosiban will be performed throughout this study.~~ Infants exposed to retosiban in utero will be followed for ~~up to~~ **a minimum of** 5 years in a separate follow-up study to assess ~~long-term~~ **overall** safety and neurodevelopmental outcomes. **Unblinded safety data will be monitored by an IDMC.**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
	clinical trials to date have not indicated that retosiban has access to the maternal or fetal CNS; however, this has not been rigorously investigated. **The short half-life of retosiban (~2 hours) is expected to minimize any significant risk.**	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Neonatal exposure via breast milk	**There were no effects on offspring growth and development in monkey reproductive toxicology studies, where systemic exposure to retosiban reached 14-fold the maximum clinical exposures. These findings suggest that exposure to retosiban during pregnancy had no adverse effect on breast milk or feeding.** While there are no clinical data on the degree of retosiban transfer into breast milk, the available data based on physiochemical properties suggest retosiban will be excreted into breast milk if dosed close to or during the time of milk production. ~~Retosiban has a 2-hour elimination half-life and is almost completely removed from the body 12 hours after termination of the infusion.~~ Given the rapid clearance of retosiban, the risk for neonatal drug exposure via breast milk appears low but could occur in the situation where the infant is fed breast milk/colostrum produced within 12 hours of the end of the infusion. ~~However, this circumstance seems unlikely as prematurity has been shown to delay the onset of milk production relative to term deliveries [Cregan, 2002; Henderson, 2008].~~ **Since lactogenesis is typically delayed 30 to 48 hours postpartum in mothers going to term (and is further delayed in mothers who deliver preterm), it seems unlikely that any drug would be in the plasma postpartum to transfer into the milk.**	Breast milk/colostrum samples will be collected for measurement of retosiban when delivery occurs and lactation has started within 12 hours of receiving study treatment infusion. • When breast milk/colostrum is produced prior to 4 hours of the completion or discontinuation of the study treatment, a sample will be collected for evaluation, and consumption by the baby is not permitted. • When breast milk/colostrum is produced between 4 and 12 hours of the completion or discontinuation of the study treatment, a sample will be collected for evaluation, and the remainder of the breast milk can be consumed if the potential benefits to the infant are believed to outweigh the potential risks. The subject should be advised on the potential risks associated with feeding the infant her breast milk/colostrum that was expressed within 12 hours of the completion or discontinuation of the study treatment. • When breast milk is produced more than 12 hours after the completion or discontinuation of study treatment, no samples will be collected for evaluation and there will be no restrictions on consumption, given that this time frame is beyond 5 half-lives of retosiban. **Safety monitoring for signals indicating adverse effects in infants following exposure to retosiban via breastfeeding will be performed throughout the study.** **Unblinded safety data will be monitored by an IDMC, including infants exposed to retosiban via breastfeeding.**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Uterine atony and postpartum hemorrhage due to oxytocin receptor antagonism	Retosiban is a competitive oxytocin antagonist whose effects can be reversed by oxytocin agonists. Retosiban has a short elimination half-life (approximately 2 hours) and is rapidly removed from the body. **Given the rapid clearance of retosiban, the risk for uterine atony appears low and would most likely occur in the situation where delivery occurs within 24 hours of treatment.** **The available clinical data for other oxytocin antagonists suggest the adverse effects of atony and postpartum hemorrhage are limited [Valenzuela, 1995; Thornton, 2009].** In monkey reproductive toxicology studies, where retosiban systemic exposure reached up to 14-fold of the maximum clinical exposures, there were no observations of postpartum hemorrhage. However, all monkey infants whose mothers received retosiban were born about 4 to 5 days after end of dosing. During the Phase II Study, OTA105256, 2 cases of postpartum hemorrhage were reported in subjects treated with retosiban. Both cases had confounding circumstances, as follows: One event occurred <48 hours from drug discontinuation and 2 hours after delivery in a subject with a prior history of retained placenta in a previous 23-week preterm delivery of twins. A history of retained placenta is a known risk factor for recurrent retained placenta. [Stones, 1993; Endler, 2012]. The other event occurred >30 days after ~~drug exposure~~ **discontinuation of retosiban**. **The incidence of primary PPH (within 24 hours of**	Given the rapid clearance of retosiban, the risk for uterine atony appears low and would most likely occur in the situation where delivery occurs within 24 hours of treatment. Investigators will be advised to refer to practice guidelines for treatment and/or management of postpartum hemorrhage, using agents approved for postpartum hemorrhage. These include oxytocin agonists and prostaglandin analogs. Retained placenta and ~~postpartum hemorrhage~~ **PPH** are AEs of special interest requiring the collection/assessment of risk factors for PPH, eCRFs for any event of PPH, and clinical parameters related to PPH. Evaluations will include outcomes such as time from delivery to expulsion of placenta and estimated blood loss. **Unblinded safety data will be monitored by an IDMC.**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
	delivery) is estimated to be between 4% to 6% of mothers who delivered [ACOG Practice Bulletin No. 76, 2006].	
Adverse maternal, fetal, or neonatal outcomes due to prolonging pregnancy in the presence of subclinical intrauterine infection	The study population includes women, particularly those presenting in labor prior to $30^{0/7}$ weeks of gestation, in whom intrauterine infection is implicated as a major etiologic factor. Infection may be chronic and asymptomatic with the first indication being preterm labor or rupture of the membranes. The asymptomatic nature of intrauterine infection, including lack of fever, abdominal pain, and fetal tachycardia, makes the diagnosis challenging. Infection is thought to trigger the labor process as a protective means for both the mother and baby [Goldenberg, 2002].	The protocol will exclude women with a temperature >100.4°F (38°C) for more than 1 hour or ≥101°F (38.3°C), as well as women with confirmed or suspected contraindication for continuation of pregnancy, such as chorioamnionitis, premature rupture of membranes, and abruption. **Placental tissue samples will be collected in study 200721 (ZINN) when delivery occurs at an investigative center to examine safety and efficacy outcomes in subjects with subclinical intrauterine infection.** A set of AEs of special interest identified in the literature as linked to maternal clinical or subclinical infection has been generated and will be used to collect targeted information of these AEs. This information will be monitored in stream by an IDMC. The unblinded IDMC will review all available safety and efficacy data.
Potential drug-drug interaction with inhibitors of BCRP or P-gp	Retosiban is a substrate of murine BCRP and P-gp *in vitro*. Inhibitors of BCRP and P-gp have the potential to increase exposure of retosiban when co-administered. BCRP and P-gp is expressed in placental membranes and the blood-brain barrier, and there is the potential of increased maternal CNS and fetal exposure to retosiban when co-administered with inhibitors. Clinical experience with exposures 10-fold higher than the exposure at the planned therapeutic dose has shown retosiban to be safe and well tolerated, with no observed untoward effects in adult women of childbearing potential.	Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure. The impact of concomitant use of retosiban with inhibitors of BCRP or P-gp will be assessed through AE monitoring. Analysis of maternal serum and cord blood samples will be performed when delivery occurs within 12 hours of study treatment infusion with co-administration of a BCRP or P-gp inhibitor to assess the effect of P-gp inhibition on placental transfer of retosiban.
Potential drug-drug interaction: Increased exposure of	**In a clinical study with healthy subjects, co-**	**Administration of strong CYP3A4 inhibitors**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
retosiban when co-administered with inhibitors of CYP3A4	**administration of retosiban with ketoconazole (a strong CYP3A4 inhibitor) increased the Cmax and AUC of retosiban, 5.2- and 8.7-fold, respectively.**	**concomitantly with IP requires an adjustment to the retosiban dosing regimen (see Section 6.3.2 and the IB). Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure.**
Potential drug-drug interaction: Decreased exposure of retosiban when co-administered with inducers of CYP3A4	**In healthy, nonpregnant females, co-administration of intravenous retosiban with efavirenz (a moderate CYP3A4 inducer) increased the clearance of retosiban by 42% and reduced total exposure by 30% and peak exposure by about 20%.**	**Administration of strong CYP3A4 inducer concomitantly with IP requires an adjustment to the retosiban dosing regimen (see Section 6.3.2 and the IB). Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure.**
Potential decreased therapeutic effect of drugs metabolized by CYP3A4 when co-administered with retosiban	**Evidence of metabolic auto-induction has been observed with repeat intravenous dosing of retosiban in women with preterm labor, as well as in healthy nonpregnant women given repeat oral doses of retosiban over 2 weeks.**	**As 48-hour administration of retosiban has the potential to increase the rate of metabolism of drugs metabolized by CYP3A4, it is recommended that these drugs be monitored for a decrease in their therapeutic effect. Details are provided in the IB. Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure.**

AE = adverse event; AUC = area under the plasma concentration time curve; BCRP = breast cancer resistance protein; Cmax = maximum plasma concentration; CNS = central nervous system; eCRF = electronic case report form; CYP3A4 = cytochrome P450 3A4 enzyme; IB = investigator's brochure; IDMC = independent data monitoring committee; P-gp = P-glycoprotein; PPH = postpartum hemorrhage; ~~SPM = Study Procedures Manual~~.

Table 2 Potential Safety Concerns

Potential ~~Risk of Clinical Significance~~ Safety Concern	Summary of Data/Rationale for ~~Risk~~ Concern	Mitigation Strategy
Other		
Pulmonary edema	Pulmonary edema is a rare but potentially life-threatening complication of pregnancy. In the setting of preterm labor, pulmonary edema is thought to involve both increased hydrostatic pressure and altered vascular permeability. Factors associated with pulmonary edema include spontaneous preterm labor, multifetal pregnancy, chorioamnionitis, pre-eclampsia, cardiac disease, fluid overload, blood transfusion, corticosteroid therapy, and tocolytic treatment. Magnesium sulfate is implicated especially when additional risk factors are present. Randomized studies have not shown an increased risk of pulmonary edema or other serious maternal complications with antenatal magnesium sulfate [Doyle, 2009; Conde-Agudelo, 2009; Bain, 2013]. A retrospective chart review showed that contributing factors for pulmonary edema during magnesium sulfate treatment included high dose, high infusion rate, high net positive fluid balance, concomitant tocolysis, and multifetal gestations [Samol, 2005].	Women with identified risk factors for pulmonary edema are excluded from the clinical study. These include multifetal pregnancies, pre-eclampsia, chorioamnionitis, and certain pre-existing cardiovascular conditions. ~~Magnesium sulfate will be administered in a standardized regimen per the investigator's discretion (see Section 6.11.1.2). Additional information regarding appropriate monitoring of magnesium sulfate therapy is provided in the SPM.~~ **Combination administration of a tocolytic is not permitted in the clinical studies.** **Maintenance tocolysis is not allowed.** Guidance is provided to investigators regarding fluid balance up to the time of starting treatment and for the duration of treatment (see Section 7.4.8). Pulmonary edema is designated as an AE of special interest requiring the collection and/or assessment of specific, relevant history and physical examination findings, targeted eCRFs to characterize any reported events, and a maximum duration of tocolytic treatment with magnesium sulfate of 48 hours.

AE = adverse event; eCRF = electronic case report form.

Section 4.6.3, Overall Benefit:Risk Conclusion

For detailed information on the identified risks and risk-benefit assessment of retosiban, refer to the IB and IB supplement 1 [GlaxoSmithKline Document Number CM2006/00201/~~03~~**05**; GlaxoSmithKline Document Number 2015N228508_00].

Section 5.1., Inclusion Criteria

1. Signed and dated written informed consent is required prior to a subject's participation in the study and the performance of any protocol-specific procedures. **At sites where enrollment of adolescents is allowed,** ~~A~~**a**dolescents aged 12 to 17 years must provide written agreement to participate in the study in accordance with applicable regulatory and country or state requirements. Subjects will also be asked to sign a release for medical records at the time of consenting to allow access to both the maternal and neonatal records including information about delivery and infant care as well as information collected prior to the consent having been signed

   NOTE: Prescreening alone does not necessarily require consent as this activity may be accomplished in the absence of study-specific procedures or assessments. In many cases, standard care and standard medical triage will provide sufficient information or evidence as to whether or not the subject is eligible for the study

2. Females aged 12 to 45 years, with an uncomplicated, singleton pregnancy and intact membranes in preterm (NOTE: Since local laws, customs, and institutional practice vary globally, investigator discretion in the enrollment of pediatric subjects is permitted**, except in Italy**)

   Italian Subjects: In Italy, the age restriction for study enrollment is 18 to 45 years.

3. Gestational age between $24^{0/7}$ and $33^{6/7}$ weeks as determined by (1) known fertilization date, either *in vitro* fertilization or intrauterine insemination, ~~-~~**or** (2) **a best estimated due** date ~~last menstrual period~~ confirmed **or established** by the earliest ultrasound ~~prior to~~ **performed before** $24^{0/7}$ weeks gestation, ~~,~~

   ~~or (3) the earliest ultrasound alone prior to $24^{0/7}$ weeks gestation, whichever is the most accurate method available for each subject.~~ In situations where prenatal ultrasound records are not available at the time the subject presents, the investigator **may enroll the subject using** the ~~will make every effort to obtain these records (either via computer records, directly from the subject's primary care obstetrician, or via telephone). However, in cases in which these records are not readily available (e.g., off hours, holiday), it is within the investigator's discretion to use~~ GA based on a verbal history from the subject with the intent of getting confirmation from the medical records **or from the subject's primary care obstetrician** as soon as possible**.**

4. Females must be diagnosed with preterm labor according to both of the following criteria **(a and b)**:

   a. Regular uterine contractions**, confirmed by tocodynamometry,** at a rate of ≥4 contractions of at least 30 seconds' duration during a 30-minute interval ~~confirmed by tocodynamometry~~**. Where tocodynamometry is not technically**

feasible, assessment by manual palpation will be permitted and must be documented.

AND ~~at least 1 of the following:~~

b. At least 1 of the following:

i.Cervical dilation ≥2 cm and ≤4 cm by digital cervical examination OR

~~e~~**ii.** If <2 cm dilation by **the required initial** digital cervical examination, a cervical change **(2 examinations must be documented) consistent with** 1 **of the following**:

- **An absolute** ~~consisting of an~~ increase of at least 25% effacement **(e.g., a change in effacement from 50% to 75%) by digital examination** or **a 10-mm decrease in cervical length by transvaginal ultrasound**

  OR

- **A** 1-cm **increase in c**ervical dilation **by digital cervical examination**

Section 5.3., Withdrawal~~/~~ **From Study, Discontinuation of IP, and** Stopping Criteria

The section describes and distinguishes the following:

- **Withdrawal of the subject from the study after randomization but before administration of IP (5.3.1.1) and after administration of IP (5.3.1.2)**
- **Discontinuation of the IP (5.3.2), wherein subjects who receive but then discontinue from IP will not be considered withdrawn from the study and should remain in the study and continue to be followed for efficacy and safety**
- **Specific stopping criteria before and during dosing, including liver function test criteria (5.3.3) and QTc findings (5.3.4).**

Section 5.3.1.1., Withdrawal From Study Participation After Randomization but Prior to Investigational Product Administration

Any subject with a nonreassuring fetal heart rate **pattern**, a uterine contraction rate less than 4 over a 30-minute interval, cervical dilation >4 cm based on digital cervical examination, abnormal levels of alanine aminotransferase (ALT) or bilirubin, or a clinically significant abnormal finding on an electrocardiogram (ECG) cannot be dosed and will be withdrawn from the study. The reasons for not dosing a subject will be recorded in the eCRF and source documents. Subjects who are withdrawn prior to receiving randomized IP will not be followed.

Sites Not in Italy: If local laboratory results are available before the start of dosing and reveal that ALT is ≥2 × the upper limit of normal (ULN) or total bilirubin is >1.5 × ULN (>35% direct bilirubin), the subject should not be dosed and should be withdrawn from

the study. An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%.

With the exception of sites in Italy, dosing may be started before local liver function test results are available. If the local laboratory results reveal liver abnormalities as defined in Section 5.3.3 and Appendix 2, study drug treatment must be discontinued.

Sites in Italy: **For sites located in Italy, dosing must not start before local laboratory liver function test results are obtained and reviewed by the investigator. If local laboratory liver function test results reveal that ALT is >2 × ULN or total bilirubin is >1.5 × ULN (>35% direct bilirubin), the subject must not be dosed and should be withdrawn from the study. An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%.**

Section 5.3.1.2., Withdrawal From Study Participation After Beginning Randomized Treatment

All subjects who are randomly assigned to and begin treatment (i.e., randomized treatment) should be encouraged to complete all phases of the study, including those who discontinue randomized treatment. However, a subject may voluntarily withdraw from study participation at any time or be withdrawn at any time at the discretion of the investigator for any maternal obstetrical or medical complications after consultation with the PPD medical monitor. If a subject withdraws from the study**,** ~~she~~ **no additional visits can occur or procedures performed, and the subject** may request destruction of any samples taken ~~and~~**;** the investigator must document this request in the site study records.

Subjects who are withdrawn after starting the Inpatient Randomized Treatment Phase but before the Post-Infusion Assessment Phase will be asked to return and complete the assessments specified for the **1-week** face-to-face post-infusion assessment visit **before withdrawing from the study** (Table 5).

Section 5.3.2., Discontinuation of Investigational Product

Subjects who receive but who discontinue from IP will not be considered withdrawn from the study and should remain in the study and continue to be followed for efficacy and safety. Once delivered, newborns will also continue to be followed for safety and outcomes through the 28 days post EDD.

A subject may voluntarily discontinue from the IP at any time. The investigator may also, at his or her discretion, discontinue the IP at any time for any medical reason or maternal or fetal complications. Subjects who discontinue randomized treatment will be managed by the investigator according to standard care.

~~Subjects who receive but who discontinue from IP will not be considered withdrawn from the study and should remain in the study and continue to be followed for efficacy and safety. Once delivered, newborns will also continue to be followed for safety and outcomes through the 28 days post EDD.~~ Subjects who discontinue the IP will not be replaced. Reasons for discontinuation from IP will be recorded in the eCRF and the subject's source documents.

Section 5.3.3., Liver Chemistry Stopping Criteria

Blood samples will be collected for central laboratory evaluation at Screening (prior to treatment), during Day 2 of the randomized treatment phase, and at the **1-week** face-to-face post-infusion assessment visit for additional liver function testing to ensure subject safety and to evaluate liver event etiology (in alignment with the US Food and Drug Administration premarketing clinical liver safety guidance); http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Sites Not in Italy: At Screening, before IP administration, ALT and bilirubin test results from a local laboratory should be obtained, although dosing may be started prior to the availability of these results. However, if the local laboratory results are available before the start of dosing and meet the following criteria, the subject should not be dosed and should be withdrawn from the study:

- ALT ≥2 × ULN OR total bilirubin >1.5 × ULN (>35% direct bilirubin). An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%.

Phase III-IV liver chemistry stopping criteria are presented in Figure 3 and Appendix 2.

The local and central laboratory liver function test results should be reviewed for the abnormalities shown in Figure 3. If the laboratory results are not available at the start of dosing and subsequent local OR central laboratory results are abnormal, dosing may be continued at the discretion of the investigator, as long as they do not exceed the liver chemistry stopping criteria shown in Figure 3 and detailed in Appendix 2.

Sites in Italy: At Screening, before IP administration, ALT and bilirubin test results from a local laboratory must be obtained and reviewed by the investigator. If the local laboratory liver function test results meet the following criteria, the subject must not be dosed and should be withdrawn from the study:

- **ALT >2 × ULN OR total bilirubin >1.5 × ULN (>35% direct bilirubin). An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%.**

Phase III-IV liver chemistry stopping criteria are presented in Figure 3 and Appendix 2.

The local and central laboratory liver function test results should be reviewed for the abnormalities shown in Figure 3. If after the start of dosing, the central laboratory results are abnormal, dosing may be continued at the discretion of the investigator, as long as they do not exceed the liver chemistry stopping criteria shown in Figure 3 and detailed in Appendix 2.

NOTE **for All Sites**: The central laboratory report will include results for ALT, aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and direct bilirubin.

Section 6.3.1., Inadequate Response

An adequate response is based on (1) a clinically relevant reduction of contraction frequency and/or intensity or (2) no change in the cervical examination. **An inadequate response is defined as a clinically significant change in the cervical examination or no significant reduction in contraction frequency and/or intensity.** . . .

Section 6.4., Managing Dose Interruptions

Temporary interruptions of the IP are permitted. The following procedures should be followed in the event of a dose interruption:

- **If the interruption is <60 minutes, restart the IP infusion.**
- **If the interruption is from 60 to 90 minutes, inclusive, administer a loading dose at a rate equal to one-half of the prior loading dose rate. For example, if the loading dose rate prior to the interruption was 240 mL/hour over 5 minutes, administer the loading dose at 120 mL/hour over 5 minutes, and then resume the infusion.**
- **If the interruption is >90 minutes, administer a loading dose at a rate equal to the prior loading dose rate. For example, if the prior loading dose was administered at 240 mL/hour over 5 minutes, administer the loading dose at 240 mL/hour over 5 minutes, and then resume the infusion.**

Any changes in the dose rate, corresponding start and stop times, and the reason for an interruption must be recorded in the eCRF.

Section 6.6., Preparation/Handling/Storage/Accountability

~~The following are the preparation instructions for the retosiban solution for infusion:~~

- ~~Withdraw 10 mL solution from a 500 mL 0.9% NaCl infusion bag and discard the solution~~
- ~~Replace discarded solution with 10 mL retosiban 15 mg/mL concentrate solution for infusion from two 5 mL vials to obtain a concentration of 0.3 mg/mL (150 mg retosiban in 500 mL 0.9% NaCl). The reconstituted product is a clear, colorless solution without particles~~
- ~~Label the IV bag with the following information: subject number, date, protocol number, dosing session number, investigator's name, and the statement, "use as directed per pharmacy manual" (for details see the Study Pharmacy Manual).~~

~~Once the vial of retosiban solution has been opened, the dilution must be performed immediately. The diluted solution for IV administration should be used within 24 hours after preparation in order to minimize the risk for microbial growth. The volume for the infusion bag must be 500 mL to avoid proportional calculations.~~

~~The unblinded pharmacist or other qualified individual will prepare the placebo admixture, which will consist of a 500-mL 0.9% NaCl infusion bag, labeled with the following information: subject number, date, protocol number, dosing session number,~~

~~investigator's name, and the statement, "use as directed per pharmacy manual." The volume of the 0.9% NaCl infusion bag should 500 mL to match the 0.9% NaCl infusion bag volume used for the retosiban admixture (for details see the Study Pharmacy Manual).~~

A description of the methods and materials required for preparation of the retosiban solution and the matching placebo are detailed in the Study Pharmacy Manual.

The following considerations must be made with regard to IP preparation, handling, storage, and accountability in this study: . . .

Section 6.12., Concomitant Medications and Nondrug Therapies

All concomitant medications taken **by the mother** during the study will be recorded in the eCRF**; the indication for the concomitant medication must be specified**. Prespecified concomitant medications of interest will be assessed. Concomitant medications taken during time of delivery and hospitalization will be obtained through a review of the hospital records.

Section 6.12.1.2., Magnesium Sulfate

Investigators have the option to use magnesium sulfate. Magnesium sulfate should be given intravenously using a 4- to 6-g loading dose and 1- to 2-g/hour infusion rate. The total duration of magnesium sulfate administration should not exceed 48 hours. **Doses exceeding this range will be considered a putative tocolytic and will be classified as a treatment failure.**

Section 6.12.2. Prohibited Medications and Nondrug Therapies

Except for IP administered during this study, no additional investigational drugs or investigational devices are permitted for the mother from the time of study entry through completion of the follow-up visit (i.e., the maternal post-delivery assessment) or 30 days after administration of the last dose of IP, whichever is longer.

The use of a pessary may be continued for subjects who were using a pessary prior to the current episode of preterm labor; however, initiating use of a pessary during the study is prohibited.

Section 6.11.2.1., Tocolytic Drugs

~~Concomitant use of calcium-channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), or β-agonists for tocolysis during IP administration is prohibited.~~ **The concomitant medications listed below will be considered putative tocolytics when administered for active preterm labor or for the prevention of preterm labor. Apart from the exceptions listed in Table 4, use of any of the following putative tocolytics at any time prior to delivery will be considered a treatment failure:**

- **Calcium-channel blockers: nifedipine**
- **β-agonists: ritodrine, terbutaline, and salbutamol**
- **NSAIDs: celecoxib, ibuprofen, indomethacin, ketorolac, naproxen**

Likewise, **subjects administered any** ~~the use of~~ **the** calcium-channel blockers, NSAIDs, or β-agonists **medications listed above** for maintenance **tocolysis (prevention of recurrent preterm labor)** ~~in subjects~~ who remained undelivered following the Inpatient Treatment Phase ~~is prohibited~~ **will be considered a treatment failure**. **Subjects administered doses of magnesium sulfate that exceed the dose specified in Section 6.12.1.2 (i.e., any dose that exceeds a 4- to 6-g IV loading dose and then a 1- to 2-g/hour infusion rate, with total duration of magnesium sulfate administration up to 48 hours) will also be considered a treatment failure.**

Table 4 Guidelines for Exceptions to Putative Tocolytic Drug Use

Drug Class	Example Drugs	Exceptions for Use
Calcium-channel blockers	nifedipine	• Administration for chronic or pregnancy-induced hypertension will not be considered a treatment failure if the indication is provided when documenting concomitant medications. • Administration for new onset of hypertension would not be considered a treatment failure. The new onset must be recorded on the AE/SAE page of the eCRF. • A dose increase due to exacerbation of hypertension will be not considered a treatment failure. Exacerbation must be recorded on the AE/SAE page of the eCRF.
β-agonists	ritodrine, salbutamol, and terbutaline	• Administration for chronic or new onset respiratory indications is permitted. Acute short-term courses for respiratory conditions will not be considered a treatment failure if the indication is provided when documenting concomitant medications. • New onset of a respiratory condition would not be considered a treatment failure. The new onset must be recorded on the AE/SAE page of the eCRF. • A dose increase due to exacerbation of a respiratory condition will be not considered a treatment failure. Exacerbation to be recorded on the AE/SAE page of the eCRF.
NSAIDs[1]	celecoxib, ibuprofen, indomethacin, ketorolac, and naproxen	• Administration for chronic medical conditions, such as rheumatoid arthritis, will not be considered a treatment failure if the indication is provided when documenting concomitant medications. • Single doses of NSAIDs not taken for treatment of preterm labor (e.g., taken for headache, dysmenorrhea, or fever) will not be considered a putative tocolytic.

NSAID = nonsteroidal anti-inflammatory drug.

1. Subjects should be discouraged from using NSAIDs without first discussing with the investigator.

Table ~~2~~5 Time and Events Table

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Post-Infusion Assessment Phase[1]		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	
	Day 0	Day 1	Day 2	~~Every week (or early termination/ withdrawal)~~ 1-week face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks ~~(±2 weeks)~~ after delivery[2]	Delivery to 28 days post EDD	Withdrawal From Study
Clinical and Other Assessments									
Written informed consent and medical releases for treatment[23]	X								
Discuss and request consent for participation in the infant follow-up study[34]		X◄	———	———	———	———	———	►X	X
Inclusion/exclusion criteria confirmation	X								
Baseline characteristics and demographic data	X								
Medical history (including obstetrics history)[45]	X								
Drug and alcohol screening[56]	X								
Physical examination (including height and weight)	X								
Cervical examination[67]	X	X	X	X					
Estimated fetal weight via ultrasound	X								

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase**[1]		**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**	**Withdrawal From Study**
	Day 0	**Day 1**	**Day 2**	~~Every week (or early termination/ withdrawal)~~ **1-week face-to-face post-infusion visit**	**Weekly post-infusion telephone call**	**Information collected via medical records review**	**6 weeks** ~~(±2 weeks)~~ **after delivery**[2]	**Delivery to 28 days post EDD**	
Determine AFI via ultrasound[7][8]	X								
Uterine contractions[8][9]	X								
Schedule post-infusion assessment visit			X						
Investigational Products[9][10]									
Retosiban or placebo		X	X						
Efficacy Assessments									
Date and time of delivery[10][11]						X			
Mode of delivery[10][11]						X			
Indication for delivery[10][11]						X			
Neonatal composite outcomes								X	
Neonatal hospital stay								X	
Maternal Safety Assessments									
Concomitant medications		X◄	———	———	———	———	►X		X
ECG 12-lead[11][12]	X								
Vital sign measurements (BP, pulse rate, temperature**, respiratory rate,** and oxygen saturation)[12][13]	X	X	X	X					

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase[1]**		**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**	**Withdrawal From Study**
	Day 0	**Day 1**	**Day 2**	~~Every week (or early termination/ withdrawal)~~ **1-week face-to-face post-infusion visit**	**Weekly post-infusion telephone call**	**Information collected via medical records review**	**6 weeks ~~(±2 weeks)~~ after delivery[2]**	**Delivery to 28 days post EDD**	
AEs, SAEs, and DREs : maternal		X◄	———	———	———	———	►X		X
Monitor fluid ~~balance~~ **intake and output**	X	X	X						
Breastfeeding status							X		
Edinburgh Postnatal Depression Scale[13~~14~~](maternal)							X		
Local laboratory assessments (LFTs only)[14~~15~~]	X								
Central laboratory assessments (including hematology, chemistry, and LFTs)[15~~16~~]	X		X	X[15~~16~~]					
Physical examination (brief)				X					
Status of postpartum bleeding							X		
Fetal Safety Assessments									
Electronic fetal ~~heart rate~~ monitoring[16]	X[17]	X[18]	X[18]	X[19]		X[20]			
AEs, SAEs, and DREs: fetal		X◄	———	———	———	———	►X		

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase**[1]		**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**	**Withdrawal From Study**
	Day 0	**Day 1**	**Day 2**	~~Every week (or early termination/ withdrawal)~~ **1-week face-to-face post-infusion visit**	**Weekly post-infusion telephone call**	**Information collected via medical records review**	**6 weeks ~~(±2 weeks)~~ after delivery**[2]	**Delivery to 28 days post EDD**	
Neonatal Safety Assessments									
AEs, SAEs, and DREs: neonatal						X ◄——— ———► X			
Neonatal Apgar Scores (1 and 5 minutes)[10][11]						X			
Neonatal growth parameters[10][11]						X			
Neonatal umbilical cord blood gases[10][11]						X			
Health Outcome Assessments									
Maternal and neonatal health care resource use[17][21]						X		X	
Pharmacokinetic Assessments									
Maternal PK blood sample[18][22]		X[18][21] ◄——— ———► X							
Cord blood sample[19][23]						X			
Breast milk/colostrum sample[20][24]						X			
Genetic and Biomarker Assessments									
Genetic blood sample for maternal DNA[21][25]	X								

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase[1]**		**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**	
	Day 0	**Day 1**	**Day 2**	~~Every week (or early termination/ withdrawal)~~ **1-week face-to-face post-infusion visit**	**Weekly post-infusion telephone call**	**Information collected via medical records review**	**6 weeks ~~(±2 weeks)~~ after delivery[2]**	**Delivery to 28 days post EDD**	**Withdrawal From Study**
Biomarker maternal blood sample[22~~26~~]	**X**								
Genetic blood sample for cell-free fetal DNA[23~~27~~]	**X**					~~X~~			
Other Assessments									
Fetal fibronectin (optional)[24~~28~~]	**X**								
Cervical length via transvaginal ultrasound (optional)[25~~29~~]	**X**								
Confirm no other study participation for infant[26~~30~~]								**X**	

AE = adverse event; AFI = amniotic fluid index; ALT = alanine aminotransferase; BP = blood pressure; DRE = disease-related event; ECG = electrocardiogram; eCRF = electronic case report form; EDD = estimated date of delivery; IP = investigational product; LFT = liver function test; PK = pharmacokinetic; SAE = serious adverse event; ULN = upper limit of normal.

1. Subjects who remain undelivered after 48 hours will return for a face-to-face post-infusion visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase. The subject will then be contacted every week via telephone to determine and record if she has delivered or experienced any subsequent episodes of preterm labor. Note: If the subject is scheduled to visit the clinic for reasons not required by this protocol and/or she happens to be present at the time the telephone assessment is due, this assessment may be completed face-to-face.

2. During the Maternal Post Delivery Assessment Phase, subjects will be contacted by telephone within 6 weeks of delivery for a post-delivery assessment, including an assessment of AEs (±2 weeks), status of breastfeeding (±2 weeks), and completion of the EPDS (±6 weeks).

~~2~~**3**. Prestudy screening information that is collected by the study site may need to come from records that are obtained before the subject has signed the informed consent. The subject will be required to provide written informed consent before any study-specific procedures are performed, and the consent will request permission for use of any information collected prior to its having been signed.

~~3~~**4**. During the study, the subject or other legal guardian for the infant (both delivered and undelivered) will be asked to give consent for the infant to participate in a separate long-term infant follow-up study for safety and neurodevelopment. Withdrawal from the study after beginning randomized treatment or discontinuing IP does not preclude involvement in the infant follow-up study.

~~4~~**5**. Medical history will be collected at Screening. If a condition with a start date predating Day 0 (Screening) is subsequently discovered, the condition should be recorded in the Medical History eCRF. For obstetrics history, the investigator will make every effort to obtain this information either via computer records, directly from the subject's primary care obstetrician, or via telephone. However, in cases in which these records are not readily available (e.g., off hours, holiday), ~~it is within~~ the investigator~~'s discretion to~~ **can** use gestational age based on the verbal history from the subject with the intent of getting confirmation from the medical records **or from the subject's primary care obstetrician** as soon as possible.

~~5~~**6**. The urine drug screen will be performed using a point-of-care qualitative testing device. A point-of-care breath analyzer for alcohol will be used in some countries in addition to the urine drug screen.

~~6~~**7**. A cervical examination (including dilation, effacement, and station) will occur at Screening, and an additional cervical examination may be performed before dosing based on investigator discretion. If a predosing cervical examination reveals dilation >4 cm, the subject cannot be dosed. Additional cervical examinations (Day 1, Day 2, and/or at the **1-week** face-to-face post-infusion assessment visit) will be performed based on investigator discretion.

~~7~~**8**. The abdominal ultrasound for determination of the AFI will be performed at Screening for all subjects.

~~8~~**9**. Uterine tocography **or manual palpation (if necessary)** will be performed prior to dosing to confirm ~~the~~ **persistent** uterine contraction**s** ~~frequency~~. If the examination reveals **in the 60 minutes before IP dosing** a rate that is <4 contractions **of a least 30 seconds' duration** over a 30-minute interval, the subject cannot be dosed. **Manual palpations will be permitted if there are technical challenges with measuring contraction frequency.**

~~9~~**10**. If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours. A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least 7 days prior to study enrollment. Investigators have discretion to use a standardized regimen of magnesium sulfate, as well as intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection.

~~10~~**11**. Information regarding delivery will be obtained through a review of the hospital and medical records. Growth parameters include neonatal weight, length, and head circumference.

~~11~~**12**. A 12-lead ECG will be performed prior to dosing. If the results are interpreted by the investigator to have clinically significant abnormalities, the subject cannot be dosed.

~~12~~**13**. Blood pressure, pulse rate, **respiratory rate,** and temperature will be assessed at Screening ~~once every 4 to 8 hours~~, as part of maternal safety monitoring during the Inpatient Randomized Treatment Phase, and at the post-infusion assessment visit. ~~Oxygen saturation will be assessed by pulse oximetry at Screening and once every 4 to 8 hours~~ ~~D~~**D**uring the Inpatient Randomized Treatment Phase, vital signs **and oxygen saturation will be assessed and recorded within the following windows relative to the start of the infusion: 15 to 30 minutes, 4 to 8 hours, 20 to 24 hours, at the end of the infusion, at the time of any dose changes, and as warranted by a medical condition.** ~~; o~~**O**xygen saturation less than 92% should be recorded as an AE or SAE, as appropriate.

~~13~~**14**. Maternal subjects will complete the Edinburgh Postnatal Depression Scale, a self-reported questionnaire, at the maternal follow-up assessment 6 weeks (~~±2~~**6** weeks) after delivery.

~~14~~**15**. The LFTs should be ordered from the local laboratory to confirm that ALT is not ≥2 × ULN OR total bilirubin is not >1.5 × ULN (>35% direct bilirubin) before dosing with the IP. An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%. **With the exception of sites in Italy,** ~~S~~**s**creening LFT laboratory results do not need to be available for the subject to be randomly assigned to treatment; however, see Section 5.3.3 if ALT or bilirubin is abnormal. **Sites in Italy**: **Subjects must not be dosed before local laboratory LFT results are obtained and reviewed by the investigator, see Section 5.3.1.1 and Section 5.3.3 for details**.

~~15~~**16**. Hematology, chemistry, and LFTs will be determined through a central laboratory at the screening, Day 2, and the **1-week** face-to-face post infusion assessment visits. The LFT values from the central laboratory should be reviewed for abnormalities (see Section 5.3.3). For subjects who deliver within 24 hours after completion or discontinuation

of IP and for subjects who deliver at the investigative center after discharge but before the **1-week** face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and LFTs should be performed. **For subjects that do not deliver at the investigative center, central laboratory assessments for hematology, chemistry, and LFTs should be performed at the investigative center within 1 week (acceptable range: 3 to 14 days) after completion of the study drug infusion.**

~~16~~**17.** Prior to dosing, if the fetal heart rate **pattern** is nonreassuring, the subject cannot be dosed.

18. **Electronic** fetal ~~heart rate~~ **monitoring is required for a minimum of 6 hours from the start of the infusion or from the start of a dose increase** ~~will be continuous throughout the Inpatient Randomized Treatment Phase. The fetal heart rate will be recorded in the eCRF once every 4 to 8 hours in conjunction with maternal vital signs. If the subject has not delivered at the end of the Inpatient Randomized Treatment Phase, fetal heart rate will be recorded at the face-to-face post-infusion assessment visit. Any fetal heart rate assessment of Category II or III will be reported as an AE of special interest on a specified eCRF (details in Section 7.4.4).~~ **As long as the fetal heart rate pattern is consistently reassuring throughout the required 6-hour duration of monitoring and the contraction frequency is ≤2 in a 30-minute window within the last hour of monitoring, continuous monitoring may be discontinued and nonstress tests initiated at a minimum of every 8 hours and as needed. Electronic fetal monitoring, including the fetal heart rate and fetal heart rate category, will be recorded in the eCRF with maternal vital signs. Any fetal heart rate assessment of Category II or III will be reported as an AE of special interest on a specified eCRF (details in Section 7.4.4).**

19. If the subject has not delivered at the end of the Inpatient Randomized Treatment Phase, fetal heart rate will be recorded at the **1-week** face-to-face post-infusion assessment visit. Any fetal heart rate assessment of Category II or III will be reported as an AE of special interest on a specified eCRF (details in Section 7.4.4).

20. **During the Delivery Phase, fetal heart rate just prior to delivery will be collected, if available, from review of delivery records. Any fetal heart rate assessment of Category II or III will be reported as an AE of special interest on a specified eCRF (details in Section 7.4.4).**

~~17~~**21**. Maternal and neonatal health care resource use may include, but is not limited to, neonatal complications requiring intensive or specialized care, neonatal hospital readmission, and neonatal ambulatory surgery.

~~18~~**22**. PK samples will be taken at each of the following sampling windows (relative to the start of the infusion on Day 1): 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 54 hours. In addition, a PK sample should be taken at the onset of any maternal or fetal SAE that occurs within 12 hours after completion or discontinuation of IP.

~~19~~**23**. In subjects who deliver at an investigative center within 12 hours following completion or discontinuation of the IP, a single cord blood sample will be collected for PK analysis. **Additionally, a maternal blood sample should be collected at the same time as the cord blood sample if the sample time does not already coincide with a PK sampling window (see Section 7.6.1).**

~~20~~**24**. A breast milk/colostrum sample is only to be collected in women who deliver and produce breast milk within 12 hours after completion or discontinuation of the IP.

~~21~~**25**. All participating investigational centers will collect a blood sample for maternal DNA in women who provide informed consent for genetic research.

~~22~~**26**. All participating investigational centers will collect a maternal blood sample for biomarker research.

~~23~~**27**. Only US and Canadian investigational centers will collect a maternal blood sample for cell-free fetal DNA in women who provide informed consent for genetic research.

~~24~~**28**. Fetal fibronectin results will be collected only at those institutions that perform fetal fibronectin testing as routine practice. Fetal fibronectin will not be used to determine study eligibility.

~~25~~**29**. Cervical length determined by transvaginal ultrasound will be collected only at those institutions that measure cervical length as routine practice. Cervical length will not be used to determine study eligibility.

~~26~~**30**. Obtain confirmation from the subject or the legal guardian for the infant that the infant is not participating in any other study.

Section 7.2., Screening and Critical Assessments Prior to Investigational Product Administration

The following assessments are required before dosing (i.e., before initiating randomized treatment):

- **Electronic** ~~F~~**f**etal ~~heart rate~~ monitoring to confirm that the fetal heart rate **pattern** remains reassuring
- Cervical examination to ensure cervical dilation **continues to** meet~~s~~ eligibility criteria at the discretion of the investigator, as clinically indicated
- Uterine tocography **or manual palpation (if necessary)** to **confirm persistent uterine contractions (see Section 5.1). A** ~~that the~~ uterine contraction frequency **that** exceeds the threshold for eligibility ~~(see Section 5.1)~~ **should be clearly documented, specifically demonstrating within the 60 minutes before IP administration that there is an observed 30-minute interval with ≥4 contractions of at least 30 seconds' duration. Manual palpations of contractions will be permitted if there are technical challenges with measuring contraction frequency; use of manual palpations must be documented. Dosing should not be started if contraction frequency decreases.**
- Liver function tests from a local laboratory to confirm that ALT is not ≥2 × ULN OR total bilirubin is not >1.5 × ULN (>35% direct bilirubin), if available~~; dosing may be started prior to the availability of these results~~. An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35% (see Section 5.3.3). **With the exception of sites in Italy, dosing may be started prior to the availability of these results.**

  Sites in Italy: Dosing must not be started prior to the availability of liver function tests results from a local laboratory (see Section 5.3.3).
- Electrocardiogram that is interpreted by the investigator to not have any significant abnormalities that may place the subject at risk for a cardiopulmonary complication during the study

If the fetal heart rate **pattern** is nonreassuring, the uterine contraction rate is less than 4 contractions over a 30-minute interval, cervical dilation exceeds 4 cm, levels of ALT or bilirubin are abnormal, or the ECG has been interpreted to have clinically significant abnormalities, the subject cannot be dosed and will be withdrawn from the study (see Section 5.3.1).

Section 7.3.1.2., Time to Treatment Failure

Treatment failure will be defined as the administration of any putative tocolytic medication **for active preterm labor or as prevention of preterm labor**, such as calcium-channel blockers, NSAIDs, or β-agonists, **apart from the exceptions listed in Table 4, and magnesium sulfate doses that exceed a 4- to 6-g IV loading dose and 1- to 2-g/hour infusion rate and total duration of magnesium sulfate administration greater than 48 hours (see Section 6.12.1.2)**. The time to treatment failure will be

assessed from the start of study treatment administration (time 0) in the Inpatient Randomized Treatment Phase until a putative tocolytic is administered.

Treatment failure will be considered to have occurred in the following situations:

- Administration of a **putative** tocolytic following IP discontinuation during the Inpatient Randomized Treatment Phase.
- Administration of a **putative** tocolytic in an undelivered subject for the management of recurrent preterm labor.
- Maintenance tocolysis is prohibited (Section 6.12.2.1); ~~however,~~ any subject treated with a tocolytic as maintenance treatment during the Post-infusion Assessment Phase will be considered a treatment failure.

For this efficacy assessment, the following information will be collected:

- Date and time of administration of any putative tocolytics
- Name and dose of the putative tocolytics
- Reason for administration of putative tocolytics

Operational procedures will be instituted to optimize data collection and reporting consistency in those situations when the subject is administered an alternative **putative** tocolytic by her referring primary care obstetrician. Details of these procedures are provided in the SPM.

Section 7.4.1.4., AEs of Special Interest

Maternal, fetal, and neonatal AEs of special interest are listed in Section 3 and in Appendix 4. **Guidelines for reporting these events are provided in Appendix 5.**

Section 7.4.2., Physical Examinations

An admission physical examination will include at a minimum maternal height, weight, and assessment of heart, lungs, abdomen, and cervical examination including dilation, effacement, and station.

A brief physical examination, assessing heart, lungs, **and** abdomen, **at a minimum,** and, if undelivered, a cervical examination at ~~a minimum~~ **the discretion of the investigator** will be performed at the **1-week** face-to-face post-infusion assessment visit, following conclusion of the treatment phase.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Section 7.4.3., Vital Signs and Oxygen Saturation

Blood pressure, pulse rate, **respiratory rate,** and temperature will be measured at the following time points during the study: Screening, Inpatient Randomized Treatment Phase ~~(once every 4 to 8 hours and as warranted by a medical condition or AE),~~ and at

the **1-week** face-to-face post-infusion assessment visit. **During the Inpatient Randomized Treatment Phase, vital signs and oxygen saturation will be assessed and recorded within the following windows relative to the start of the infusion: 15 to 30 minutes, 4 to 8 hours, 20 to 24 hours, at the end of the infusion, at the time of any dose changes, and as warranted by a medical condition.** Subjects may be either in a semirecumbent or seated position. ~~In addition, oxygen saturation will be assessed by pulse oximetry at Screening and during the Inpatient Randomized Treatment Phase (once every 4 to 8 hours with the other vital sign assessments).~~ Clinically relevant abnormal findings, including oxygen saturation less than 92%, should be recorded as an AE or SAE, as appropriate.

Section 7.4.4., Electronic Fetal ~~Heart Rate~~ Monitoring

Electronic fetal monitoring is required for a minimum of 6 hours from the start of the infusion or from the start of a dose increase if the following are confirmed during monitoring:

- **The fetal heart rate pattern is consistently reassuring throughout the required minimum 6-hour duration of monitoring**
- **The contraction frequency is ≤2 in a 30-minute window within the last hour of monitoring.**

A reassuring nonstress test (defined as meeting Category I criterion), accounting for GA expectations, is required at a minimum of every 8 hours and as needed. An additional 6 hours of electronic fetal monitoring will be required for dose interruptions that are sufficiently long as to require an additional infusion of the IP.

Electronic fetal monitoring, including the ~~F~~fetal heart rate **and fetal heart rate category,** ~~will be monitored continuously from Screening until completion of the 48-hour Inpatient Randomized Treatment Phase. Subjects will be allowed breaks of up to 1 hour if fetal heart rate monitoring up to that point has been reassuring. Fetal heart rate~~ should be recorded in the eCRF ~~once every 4 to 8 hours~~ at approximately the same time that maternal vital sign measurements are collected (Section 7.4.3). **The electronic fetal heart rate tracing (paper or electronic) must be archived and retained in site records.** Fetal heart rate ~~also~~ will be recorded at the **1-week** face-to-face post-infusion assessment visit if the subject remains undelivered. During the Delivery Phase, fetal heart rate **just prior to delivery** ~~monitoring information~~ will be ~~collected~~ **summarized, if available,** from review of ~~medical~~ **delivery** records. Any fetal heart rate assessment of Category II or III according to the following criteria and based on ACOG guidelines [ACOG Practice Bulletin No. 106, 2009] will be reported as an AE of special interest on a specified eCRF in addition to the corresponding AE or SAE eCRF:

Section 7.4.6., Clinical Safety Laboratory Assessments

With the exception of the above, all protocol-required laboratory assessments must be performed by the central laboratory. **For subjects that do not deliver at the investigative center, central laboratory assessments for hematology, chemistry, and LFTs should be performed at the investigative center within 1 week (acceptable range: 3 to 14 days) after completion of the study drug infusion.**

Section 7.4.8., Fluid Management

Care should be taken to assess for fluid overload by monitoring the total fluid ~~balance~~ **intake and output** from the Screening Phase through Inpatient Randomized Treatment Phase and assessing for signs and symptoms of fluid overload. Details regarding this assessment are provided in the SPM.

Section 7.4.10., Maternal Depression

Maternal subjects will complete the EPDS at the maternal follow-up assessment 6 weeks (±~~2~~**6** weeks) post-delivery (Table 5).

Section 7.6.1, Sampling

Maternal blood samples for the quantification of retosiban in plasma will be taken at the following sampling windows (relative to the start of the infusion on Day 1): 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 54 hours, the last point being after the end of the infusion. Samples may be taken at any time within these windows, but the exact time of the sample should be recorded in the eCRF. The volume of blood required for PK sampling, as specified in the Time and Events Table (Table 5), is approximately 8 mL.

Additionally, a maternal blood sample should be collected at the same time as the cord blood sample (see Section 7.6.2) if the sample time does not already coincide with one of the PK sampling windows listed above.

~~In addition~~ A blood sample **also** should be taken at the onset of any maternal or fetal SAE that occurs within 12 hours after completion or discontinuation of IP

Section 9.3.3.3., Subgroup Analysis

Additionally, comparisons of retosiban versus placebo for co-primary and key secondary endpoints may also be performed for the following subgroups:

- GA strata $24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$, or $31^{0/7}$ to $33^{6/7}$
- Established progesterone use (yes or no)
- Magnesium sulfate use
- **Putative** ~~T~~**t**ocolytic use following IP discontinuation

Other potential subgroup comparisons will be described in the RAP.

Section 9.3.4., Interim Analyses

Two interim analyses are planned. The first interim analysis will occur after approximately 150 ~~women/newborn pairs~~ **subjects have** complete**d delivery and have time-to-delivery results available** ~~all assessments~~. The primary objective of the first interim analysis is to determine if the study should be terminated for lack of efficacy (futility) based on prespecified criteria. The decision will be based primarily on the

analysis of the key secondary endpoint of time to delivery; however, all available safety and efficacy data will be reviewed.

. . .

The second interim analysis will occur after approximately 400 women/newborn pairs **are followed up to 28 days post EDD** ~~complete all assessments~~. . .

Section 9.4.3., Health Outcomes Analyses

To further describe the health outcomes of retosiban, the following subgroups may be explored:

- GA of pregnancy at randomization
- Established progesterone use
- Magnesium sulfate use
- **Putative** ~~T~~**t**ocolytic use following IP discontinuation
- Region/sites

Section 11., References

American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Practice Bulletin No. 76. Postpartum hemorrhage. Obstet Gynecol. 2006;108(4):1039-47.

~~Cregan MD, De Mello TR, Kershaw D, McDougall K, Hartmann PE. Initiation of lactation in women after preterm delivery. Acta Obstet Gynecol Scand. 2002;81(9):870-7.~~

GlaxoSmithKline Document Number CM2006/00201/0~~3~~**5**. Investigator's brochure Version 3. APR-2014.

~~Henderson JJ, Hartmann PE, Newnham JP, Simmer K. Effect of preterm birth and antenatal corticosteroid treatment of lactogenesis II in women. Pediatrics. 2008;121(1):e92-100.~~

Thornton S, Goodwin TM, Greisen G, Hedegaard M, Arce JC. The effect of barusiban, a selective oxytocin antagonist, in threatened preterm labor at late gestational age: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol. 2009;200(6):627e1-627e10.

Valenzuela GJ, Craig J, Bernhardt MD, Holland ML. Placental passage of the oxytocin antagonist atosiban. Am J Obstet Gynecol.l 1995;172(4 Pt 1):1304-6.

Section 12.1., Appendix 1: Abbreviations and Trademarks

Definitions

Chronological age	Defined as the time elapsed after birth; it is usually described in days, months, and years
Estimated date of delivery	Defined as $40^{0/7}$ weeks' gestation for all subjects
Gestational age	Determined by (1) known fertilization date, either *in vitro* fertilization or intrauterine insemination~~,~~ **or** (2) **a best estimated due date** ~~last menstrual period~~ confirmed **or established** by the earliest ultrasound ~~prior to~~ **performed before** $24^{0/7}$ weeks' gestation~~, or (3) the earliest ultrasound alone prior to $24^{0/7}$ weeks' gestation, whichever is the most accurate method available for each subject~~**.**
Postmenstrual age	Determined by adding chronological age to gestational age at delivery

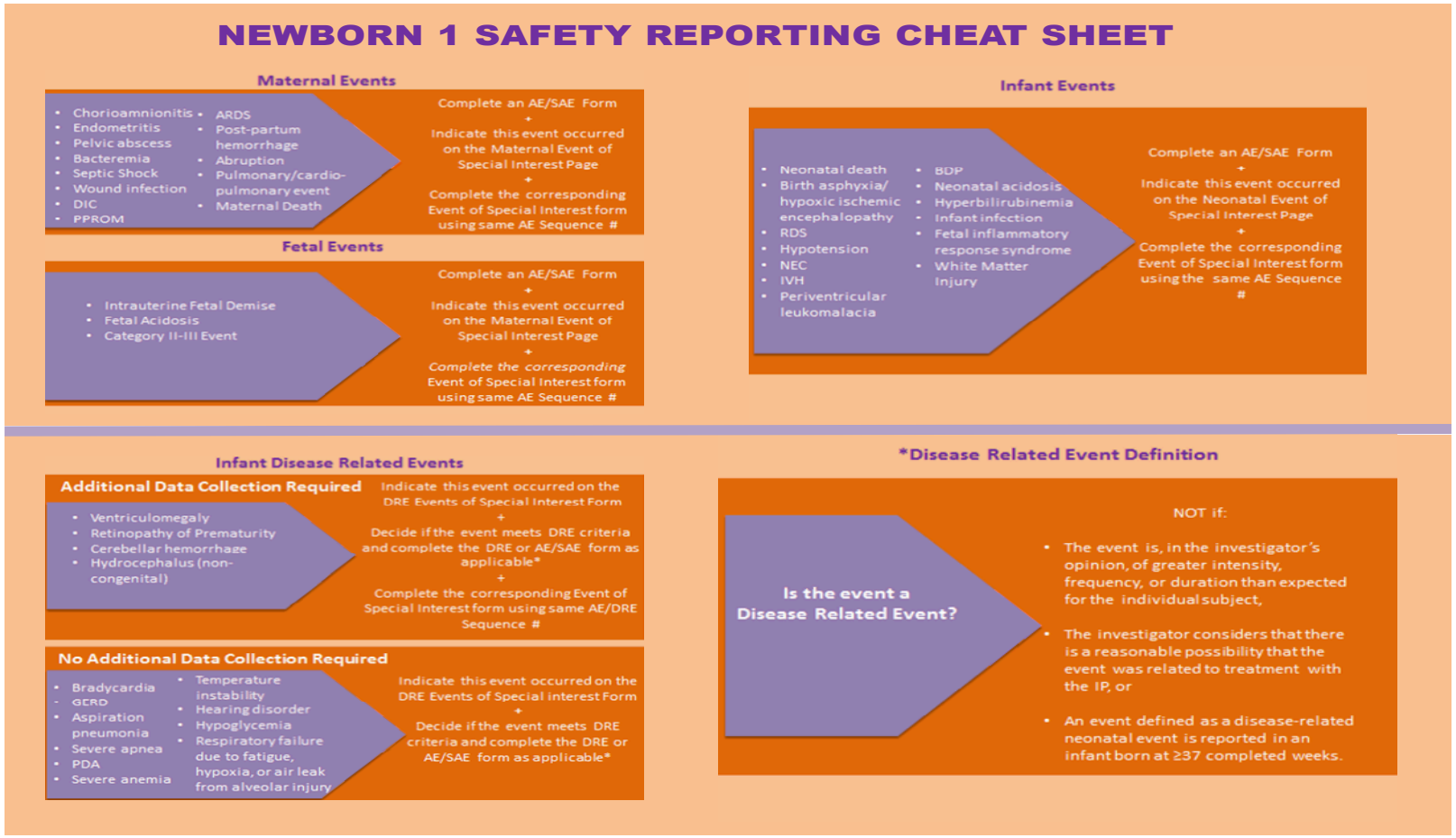
Section 12.3.5, Evaluating AEs and SAEs

Assessment of intensity:

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to **an intensity category. Refer to the SPM for details on assessing intensity of maternal and fetal AEs and SAEs.** ~~one of the following categories:~~

- ~~Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.~~
- ~~Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities~~
- ~~Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.~~
- **Note:** An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE.

Section 12.5., Appendix 5: Safety Reporting Cheat Sheet



AE = adverse event; ARDS = adult respiratory distress syndrome, BDP = bronchopulmonary dysplasia; DIC = Disseminated Intravascular Coagulation; DRE = disease-related event; GERD = gastroesophageal reflux disease, IP = investigational product; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; RDS = respiratory distress syndrome; SAE = serious adverse event.

Section 12.6., Appendix ~~5~~6: Genetic Research

Section 12.7., Appendix ~~6~~7: Cytochrome P450 3A4 Enzyme Inhibitors and Inducers

Strong[1] (Requires Adjustment to Dosing Regimen)	**Moderate[2]**	**Weak[3]**
Inhibitors		
Amprenavir	Aprepitant	Amlodipine
Atazanavir	Cimetidine	Atomoxetine
Clarithromycin	Darunavir	Atorvastatin
Conivaptan	Diltiazem	Azithromycin
Fosamprenavir	Erythromycin	Bicalutamide
Grapefruit juice[4]	Fluconazole	Chlorzoxazone
Indinavir	Imatinib	Cilostazol
Itraconazole	Nifedipine	Cyclosporine
Ketoconazole	Tofisopam	Darifenacin
Nefazodone	Verapamil	Dasatinib
Nelfinavir		Ezetimibe
Ritonavir		Fentanyl
Saquinavir		Fluvoxamine
Telithromycin		Gemfibrozil
Troleandomycin		Isoniazid
Voriconazole		Lacidipine
		Omeprazole
		Posaconazole
		Propiverine
		Propofol

Strong[1] (Requires Adjustment to Dosing Regimen)	**Moderate[2]**	**Weak[3]**
		Quinidine
		Ranitidine
		Ranolazine
		Roxithromycin
		Tabimorelin
Inducers		
Strong[1] (Requires Adjustment to Dosing Regimen)	**Moderate[2]**	**Weak[3]**
Carbamazepine	Bosentan	Aprepitant
Efavirenz	Etravirine	Amprenavir
Phenytoin	Nafcillin	Avasimibe
Rifampin	Nevirapine	Dexamethasone
St. Johns Wort	Phenobarbital	Glycyrrhizin
		Modafinil
		Oxcarbazepine
		Pioglitazone
		Prednisone
		Rifabutin
		Rufinamide

1. Strong inhibitor: >5 AUCi/AUC (area of the curve of substrate in the presence of an inhibitor/area under the curve of substrate in a control condition); strong inducer: <0.2 AUCi/AUC. **Co-administration of study drug with a strong inhibitor or strong inducer requires an adjustment to the study drug dosing regimen.**
2. Moderate inhibitor: 2 to 5 AUCi/AUC; moderate inducer: 0.2 to 0.5 AUCi/AUC.
3. Weak inhibitor: <2 AUCi/AUC; weak inducer: 0.5 to 0.8 AUCi/AUC.
4. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. However, no dose adjustment is needed for retosiban, as grapefruit juice is not expected to cause an interaction given that retosiban is administered intravenously.

Section 12.8., Appendix ~~7~~8: Country-Specific Requirements

Section 12.9., Appendix ~~8~~9: Protocol Changes

Protocol Amendment Number 05

Protocol Amendment Number 05 is applicable to all clinical study centers participating in this study. Protocol changes specified in Amendment Number 05 are summarized as follows:

- Removed screening urine drug and alcohol tests. Women with a history of overt substance abuse during the pregnancy or dependency that may have the potential to complicate the pregnancy outcome are still ineligible for the study, but instead of mandating a drug and alcohol test at the time of Screening, the investigator will be allowed to use medical discretion and knowledge of the subject to decide whether or not the subject is eligible.
- Removed the requirement that investigator confirm uterine contraction rate and cervical dilation after randomization and just before study drug administration. In place of this requirement, added that after randomization and prior to study drug administration investigators will re-assess that tocolytic therapy is still indicated, according to their medical discretion. This change has been made to simplify the Inpatient Randomized Treatment Phase and to allow the investigator to use medical judgement about whether or not the subject requires tocolysis immediately prior to study drug administration.
- Clarified that an abdominal ultrasound to assess fetal growth is needed at Screening unless the most recent ultrasound is within 3 weeks (21 days) before the date of randomization. This change has been made to avoid a repeat ultrasound if an abdominal ultrasound has already been completed within 3 weeks of the study treatment.
- Updated the list of maternal disease-related events to clarify the reporting process for events of subsequent preterm labor and hospitalization for delivery that are not worse than expected.
- Added that the amniotic fluid index should be measured using the 4-quadrant method.
- Incorporated other administrative changes. The rationale for these changes is to ensure a clear and complete protocol for use at the investigational centers.

Specific Changes in the Text

Title Page

Authors (GSK): PPD

Medical Monitor/Sponsor Information Page

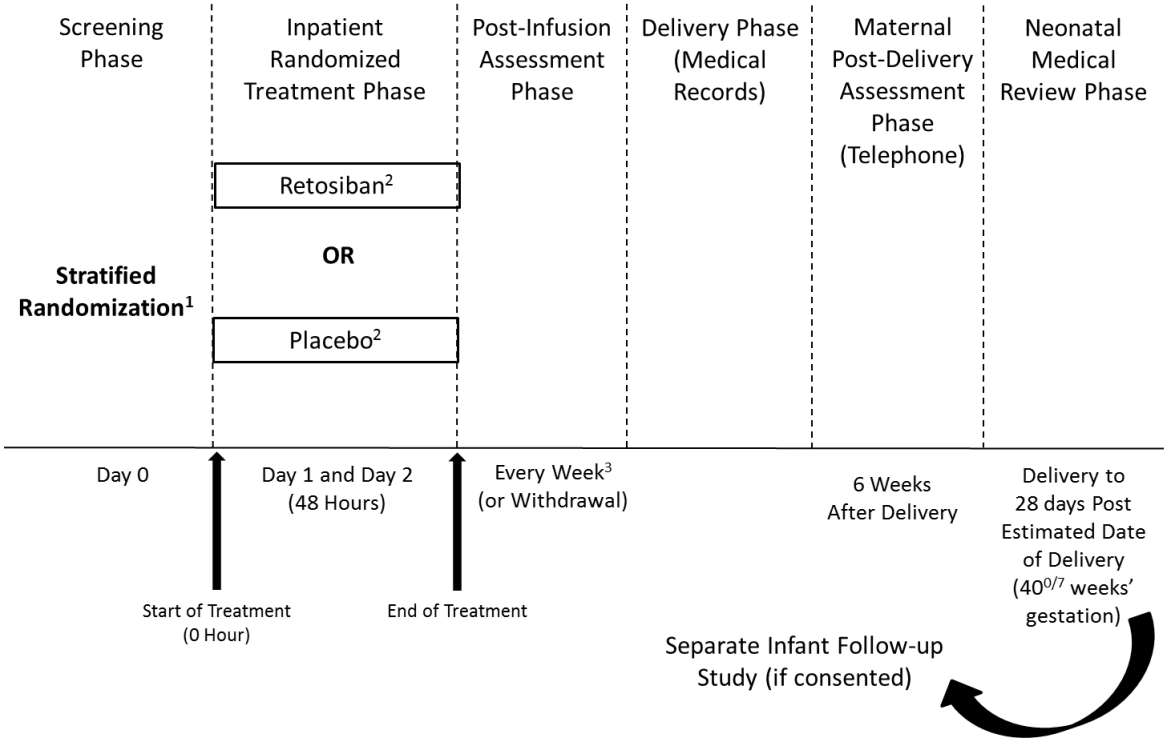
Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number	After-Hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD MD	PPD PPD	PPD PPD	PPD PPD	PPD Pharmacovigilance
Secondary Medical Monitor	PPD PPD PPD MD	PPD PPD	PPD PPD	PPD PPD	PPD Pharmacovigilance
SAE Fax Number				PPD PPD	

Section 4.2., Treatment Arms and Duration

NEWBORN-1 will comprise 6 phases: Screening, Inpatient Randomized Treatment, Post Infusion Assessment, Delivery, Maternal Post-Delivery Assessment, and Neonatal Medical Review (Figure 2). The duration of any subject's (maternal or neonatal) participation in the study will be variable and dependent on GA at study entry and the date of delivery.

Figure 2 Study Design



During the Maternal Post Delivery Assessment Phase, the subject will be contacted by telephone within 6 weeks of delivery for a post-delivery assessment, including an assessment of AEs (±2 weeks), status of breastfeeding (±2 weeks), and completion of the EPDS (**-2 weeks/+**~~=~~6 weeks).

During the Neonatal Medical Review Phase, the neonatologist subinvestigator will conduct a comprehensive review of the newborn's medical records from delivery through 28 days EDD ($40^{0/7}$ weeks' gestation) for all subjects. ~~During this phase, the subject or other legal guardian for the infant should also confirm that the infant is not participating in any other study.~~

Two interim analyses are planned. The first interim analysis will occur after approximately 150 subjects have completed delivery and have time-to-delivery results available. The second interim analysis will occur after approximately 400 women/newborn pairs are followed up to 28 days post EDD. At each interim analysis, all available safety and efficacy data will be reviewed by the unblinded

independent data monitoring committee (IDMC) who may make recommendations to terminate the study based on prespecified criteria. ~~At the second interim analysis, the IDMC may also make recommendations to increase the sample size of the study based on prespecified criteria.~~ Additionally, the IDMC may make recommendations to terminate the study at any time for an unfavorable benefit:risk profile. Subjects will continue to be enrolled while the interim analyses are being conducted.

Section 4.6.3., Overall Benefit:Risk Conclusion

For detailed information on the identified risks and risk-benefit assessment of retosiban, refer to the IB ~~and IB supplement 1~~ [GlaxoSmithKline Document Number CM2006/00201/05~~; GlaxoSmithKline Document Number 2015N228508_00~~].

Section 5., Selection of Study Population and Withdrawal Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GlaxoSmithKline (GSK) IP or other study treatment that may affect subject eligibility is provided in the IB~~, IB Supplement 1,~~ and other pertinent documents [GlaxoSmithKline Document Number CM2006/00201/05~~; GlaxoSmithKline Document Number 2015N228508_00~~].

Section 5.1, Inclusion Criteria

2. Females aged 12 to 45 years, with an uncomplicated, singleton pregnancy and intact membranes in **spontaneous** preterm **labor** (Note: This protocol includes pregnant adolescents, aged 12 to 17 years, as appropriate, unless national or local regulations restrict the age for study enrollment to subjects aged 18 to 45 years.)

Section 5.2, Exclusion Criteria

7. Women with co-morbid medical or obstetric conditions that in the opinion of the investigator have the potential to complicate the pregnancy course and outcomes, such as uncontrolled hypertension or uncontrolled diabetes (if known, history of glycosylated hemoglobin >8% at any time during pregnancy), **known or suspected maternal Zika infection during gestation (see SPM for details),** or compromise the safety of the subject, such as underlying cardiovascular disorder (specifically ischemic cardiac disease, congenital heart disease, pulmonary hypertension, valvular heart disease, arrhythmias, and cardiomyopathy)

8. Women with a history of substance abuse during the pregnancy or **dependency that may have the potential to complicate the pregnancy outcome** ~~urine drug screen positive for cocaine, phencyclidine (PCP), methamphetamine, or amphetamine~~

~~9. Women in whom the combination of history and screening test results is suggestive of abuse or dependency that may have the potential to complicate the pregnancy outcome. NOTE: Exclusion of a subject with a positive findings for substances other than cocaine, PCP, methamphetamine, or amphetamine is at the investigator's discretion (examples include alcohol, cannabinoids, and opiates)~~

~~109.~~ Women with any diagnosis, condition, treatment, or other factor that, in the opinion of the investigator, has the potential to affect or confound assessments of efficacy or safety

~~110.~~ Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment)

NOTES:

- Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice, or cirrhosis

- Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (or positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria

1**1**~~2~~. History of sensitivity to any of the IPs or components thereof or a history of drug or other allergy that, in the opinion of the investigator or PPD medical monitor, contraindicates the subject's participation

Section 5.3.1.1., Withdrawal From Study Participation After Randomization but Prior to Investigational Product Administration

Any subject with a nonreassuring fetal heart rate pattern, a **re-assessment that determines tocolytic therapy is no longer indicated (according to investigator's medical discretion),** ~~uterine contraction rate less than 4 over a 30-minute interval, cervical dilation >4 cm based on digital cervical examination,~~ abnormal levels of alanine aminotransferase (ALT) or bilirubin **(if results are available)**, or a clinically significant abnormal finding on an electrocardiogram (ECG) cannot be dosed and will be withdrawn from the study. The reasons for not dosing a subject will be recorded in the eCRF and source documents. Subjects who are withdrawn prior to receiving randomized IP will not be followed.

Section 6.5., Blinding

The IDMC will review unblinded data periodically in addition to 2 formal interim analyses in accordance with the IDMC charter. Unblinded data will be provided by an independent statistical data analysis ~~committee~~ **center**.

Section 7.1., Time and Events Table

Table 5 Time and Events Table

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Post-Infusion Assessment Phase[1]		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	1-week face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery[2]	Delivery to 28 days post EDD	
Clinical and Other Assessments									
Written informed consent and medical releases for treatment[3]	X								
Discuss and request consent for participation in the infant follow-up study[4]		X◄	———	———	———	———	———	►X	X
Inclusion/exclusion criteria confirmation	X								
Baseline characteristics and demographic data	X								
Medical history (including obstetrics history)[5]	X								
~~Drug and alcohol screening~~[6]	~~X~~								
Physical examination (including height and weight)	X								
Cervical examination[7]~~6~~	X	X	X	X					
Estimated fetal weight **and head circumference** via ultrasound[7]	X								

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase[1]**		**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**	**Withdrawal From Study**
	Day 0	**Day 1**	**Day 2**	**1-week face-to-face post-infusion visit**	**Weekly post-infusion telephone call**	**Information collected via medical records review**	**6 weeks after delivery[2]**	**Delivery to 28 days post EDD**	
Determine AFI via ultrasound[8]	X								
Uterine contractions[9]	X								
Schedule post-infusion assessment visit			X						
Investigational Products[10]									
Retosiban or placebo		X	X						
Efficacy Assessments									
Date and time of delivery[11]						X			
Mode of delivery[11]						X			
Indication for delivery[11]						X			
Neonatal composite outcomes								X	
Neonatal hospital stay								X	
Maternal Safety Assessments									
Concomitant medications		X◄	———	———	———	———	——— ►X		X
ECG 12-lead[12]	X								
Vital sign measurements (BP, pulse rate, temperature, respiratory rate, and oxygen saturation)[13]	X	X	X	X					
AEs, SAEs, and DREs : maternal		X◄	———	———	———	———	——— ►X		X
Monitor fluid intake and output	X	X	X						
Breastfeeding status							X		

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase[1]**		**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**	**Withdrawal From Study**
	Day 0	**Day 1**	**Day 2**	**1-week face-to-face post-infusion visit**	**Weekly post-infusion telephone call**	**Information collected via medical records review**	**6 weeks after delivery[2]**	**Delivery to 28 days post EDD**	
Edinburgh Postnatal Depression Scale[14](maternal)							X		
Local laboratory assessments (LFTs only)[15]	X								
Central laboratory assessments (including hematology, chemistry, and LFTs)[16]	X		X	X[16]					
Physical examination (brief)				X					
Status of postpartum bleeding							X		
Fetal Safety Assessments									
Electronic fetal monitoring	X[17]	X[18]	X[18]	X[19]		X[20]			
AEs, SAEs, and DREs: fetal		X◄	———	———	———	►X			
Neonatal Safety Assessments									
AEs, SAEs, and DREs: neonatal						X◄	———	►X	
Neonatal Apgar Scores (1 and 5 minutes)[11]						X			
Neonatal growth parameters[11]						X			
Neonatal umbilical cord blood gases[11]						X			

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Post-Infusion Assessment Phase[1]**		**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**	**Withdrawal From Study**
	Day 0	**Day 1**	**Day 2**	**1-week face-to-face post-infusion visit**	**Weekly post-infusion telephone call**	**Information collected via medical records review**	**6 weeks after delivery[2]**	**Delivery to 28 days post EDD**	
Health Outcome Assessments									
Maternal and neonatal health care resource use[21]						**X**		**X**	
Pharmacokinetic Assessments									
Maternal PK blood sample[22]		**X**[21] ◄——► **X**							
Cord blood sample[23]						**X**			
Breast milk/colostrum sample[24]						**X**			
Genetic and Biomarker Assessments									
Genetic blood sample for maternal DNA[25]	**X**								
Biomarker maternal blood sample[26]	**X**								
Genetic blood sample for cell-free fetal DNA[27]	**X**								
Other Assessments									
Fetal fibronectin (optional)[28]	**X**								
Cervical length via transvaginal ultrasound (optional)[29]	**X**								
~~Confirm no other study participation for infant[30]~~								**~~X~~**	

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2. During the Maternal Post Delivery Assessment Phase, subjects will be contacted by telephone within 6 weeks of delivery for a post-delivery assessment, including an assessment of AEs (±2 weeks), status of breastfeeding (±2 weeks), and completion of the EPDS (**-2 weeks/+**~~±~~6 weeks).
3. Prestudy screening information that is collected by the study site may need to come from records that are obtained before the subject has signed the informed consent. The subject will be required to provide written informed consent before any study-specific procedures are performed, and the consent will request permission for use of any information collected prior to its having been signed.
4. During the study, the subject or other legal guardian for the infant (both delivered and undelivered) will be asked to give consent for the infant to participate in a separate long-term infant follow up study for safety and neurodevelopment. Withdrawal from the study after beginning randomized treatment or discontinuing IP does not preclude involvement in the infant follow-up study.
5. Medical history will be collected at Screening. If a condition with a start date predating Day 0 (Screening) is subsequently discovered, the condition should be recorded in the Medical History eCRF. For obstetrics history, the investigator will make every effort to obtain this information either via computer records, directly from the subject's primary care obstetrician, or via telephone. However, in cases in which these records are not readily available (e.g., off hours, holiday), the investigator can use gestational age based on the verbal history from the subject with the intent of getting confirmation from the medical records or from the subject's primary care obstetrician as soon as possible.
6. ~~The urine drug screen will be performed using a point-of-care qualitative testing device. A point-of-care breath analyzer for alcohol will be used in some countries in addition to the urine drug screen.~~

~~7~~**6**. A cervical examination (including dilation, effacement, and station) will occur at Screening, and an additional cervical examination may be performed before dosing based on investigator discretion. ~~If a predosing cervical examination reveals dilation >4 cm, the subject cannot be dosed.~~ Additional cervical examinations (Day 1, Day 2, and/or at the 1 week face to-face post-infusion assessment visit) **are not required but** ~~will~~ may be performed based on investigator discretion. **If inclusion criteria are based on cervical change (see Section 5.1), 2 examinations must be documented (either 2 digital cervical examinations or 2 cervical length examinations).**

7. An ultrasound for estimation of fetal weight and head circumference is needed at Screening unless the date of the most recent ultrasound that includes fetal weight and head circumference is within 3 weeks (21 days) of the date of randomization.

8. The abdominal ultrasound for determination of the AFI will be performed at Screening for all subjects. **The AFI should be measured using the 4-quadrant method.**
9. Uterine tocography or manual palpation (if necessary) will be performed **at Screening** ~~prior to dosing to confirm persistent uterine contractions. If the examination reveals in the 60 minutes before IP dosing a rate that is <4 contractions of a least 30 seconds' duration over a 30-minute interval, the subject cannot be dosed~~. Manual palpations will be permitted if there are technical challenges with measuring contraction frequency.

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14. Maternal subjects will complete the Edinburgh Postnatal Depression Scale, a self-reported questionnaire, at the maternal follow-up assessment 6 weeks (**-2 weeks/+**~~±~~6 weeks) after delivery.
15. The LFTs should be ordered from the local laboratory before **dosing with the IP**. **If the local laboratory results are available before the start of dosing,** ~~to~~ confirm that ALT is not ≥2 × ULN OR total bilirubin is not >1.5 × ULN (>35% direct bilirubin) ~~before dosing with the IP~~. An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%. With the exception of sites in Italy, screening LFT laboratory results do not need to be available for the subject to be randomly assigned to treatment **or for the start of dosing with IP**; however, see Section 5.3.3 if ALT or bilirubin is abnormal. Sites in Italy: Subjects must not be dosed before local laboratory LFT results are obtained and reviewed by the investigator, see Section 5.3.1.1 and Section 5.3.3 for details.

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~~30. Obtain confirmation from the subject or the legal guardian for the infant that the infant is not participating in any other study.~~

Section 7.2., Screening and Critical Assessments Prior to Investigational Product Administration

The following assessments are required before dosing (i.e., before initiating randomized treatment):

- Electronic fetal monitoring to confirm that the fetal heart rate pattern remains reassuring
- **Re-assess that tocolytic therapy is still indicated, according to the investigator's medical discretion.**
- ~~Cervical examination to ensure cervical dilation continues to meet eligibility criteria at the discretion of the investigator, as clinically indicated~~
- ~~Uterine tocography or manual palpation (if necessary) to confirm persistent uterine contractions (see Section 5.1). A uterine contraction frequency that exceeds the threshold for eligibility should be clearly documented, specifically demonstrating within the 60 minutes before IP administration that there is an observed 30-minute interval with ≥4 contractions of at least 30 seconds' duration. Manual palpations of contractions will be permitted if there are technical challenges with measuring contraction frequency; use of manual palpations must be documented. Dosing should not be started if contraction frequency decreases.~~
- Liver function tests from a local laboratory to confirm that ALT is not ≥2 × ULN OR total bilirubin is not >1.5 × ULN (>35% direct bilirubin), if available. An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35% (see Section 5.3.3).With the exception of sites in Italy, dosing may be started prior to the availability of these results.

  Sites in Italy: Dosing must not be started prior to the availability of liver function tests results from a local laboratory (see Section 5.3.3).
- Electrocardiogram that is interpreted by the investigator to not have any significant abnormalities that may place the subject at risk for a cardiopulmonary complication during the study

If the fetal heart rate pattern is nonreassuring, **tocolytic therapy is no longer indicated** ~~the uterine contraction rate is less than 4 contractions over a 30 minute interval, cervical dilation exceeds 4 cm~~, levels of ALT or bilirubin are abnormal **(if results are available)**, or the ECG has been interpreted to have clinically significant abnormalities, the subject cannot be dosed and will be withdrawn from the study (see Section 5.3.1).

Section 7.4.1.7., Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The DREs listed in Section 7.4.1.7.1 and Section 7.4.1.7.2 will be monitored by ~~a safety review team made up of~~ an internal GSK safety **review** team (reviewing blinded data) ~~and the IDMC (reviewing unblinded data)~~.

Section 7.4.1.7.1., Disease-Related Maternal Events

The following DREs are common maternal events during pregnancy, labor, and delivery:

- Signs and symptoms of labor discomfort (e.g., cramping, backache, muscle aches, nausea)
- **Subsequent episodes of preterm labor (even if hospitalization is required) unless 1 of the conditions listed at the end of Section 7.4.1.7.2 applies**
- **Hospitalization for delivery, unless prolonged or 1 of the conditions listed at the end of Section 7.4.1.7.2 applies**

Section 7.4.1.7.2., Disease-Related Neonatal Events (Occurring in Infants Born Prior to 37 Completed Weeks)

Because these events (Section 7.4.1.7.1 and Section 7.4.1.7.2) are typically associated with preterm labor and prematurity, they will not be reported according to the standard process for expedited reporting of SAEs to GSK/PPD (even though the event may meet the definition of a SAE). These events will be recorded on the DRE page in the eCRFs, and additional data will be recorded for any DREs related to study endpoints (see Section 3). These DREs will be monitored by the ~~IDMC and~~ internal **GSK** safety review team.

Section 7.4.5., Abdominal Ultrasound

An abdominal ultrasound for determination of the AFI will be performed at Screening for confirmation that subject does not have evidence of polyhydramnios or oligohydramnios (per exclusion criterion 6, Section 5.2). **The AFI should be measured using the 4-quadrant method (see SPM for details).** An abdominal ultrasound to assess fetal growth will be done at Screening (unless records are available documenting an ultrasound derived estimated fetal weight **and head circumference** within ~~1~~**3** week**s** of Screening, with the results and date of assessment recorded in the eCRF).

Section 7.4.6., Clinical Safety Laboratory Assessments

The following laboratory tests will be performed locally:

- Liver function tests, including ALT and bilirubin, performed at Screening (see Section 5.3.3)
- ~~Urine drug screen using a point-of-care, qualitative testing device~~
- ~~Alcohol screen using point-of-care breath analyzer; in some countries this will be in addition to the urine drug screen~~

Section 7.4.10., Maternal Depression

The effect of preterm birth on maternal health status will be assessed using the EPDS. The EPDS is a 10-item self-reported assessment of depression, validated for administration during both the antenatal and the post-natal periods. Items are rated on a 4-point variable Likert scale, ranging from 0 to 3. A score of 12+ indicates an increased probability of depression and investigators or designated investigative center personnel will be notified immediately. Certain items in the scale also assess anxiety and will be used to assess level of anxiety. Maternal subjects will complete the EPDS at the maternal follow-up assessment 6 weeks (**-2 weeks/+**~~±~~6 weeks) post-delivery (Table 5).

Section 9.1., Hypotheses

No further adjustments to the type I error rate are planned for the co-primary endpoints. Details of the methodologies to control the type I error will be included in the IDMC **charter** and study reporting and analysis plans (RAPs).

Section 11, References

~~GlaxoSmithKline Document Number 2015N228508_00. Investigator's brochure Version 3 Supplement 1. FEB-2015.~~

GlaxoSmithKline Document Number CM2006/00201/05. Investigator's brochure ~~Version 3. APR-2014~~ **GSK716755. 29-Jun-2016**.

Section 12.1, Appendix 1: Abbreviations and Trademarks

~~PCP phencyclidine~~