

TITLE PAGE

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Title:	Randomized, Double-blind, Multicenter, Phase III Study Comparing the Efficacy and Safety of Retosiban Versus Atosiban Therapy for Women in Spontaneous Preterm Labor
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Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2014N194185_00	2014-MAY-14	Original
2014N194185_01	2015-JAN-29	Country-Specific Protocol Amendment for Applicable Sites in France
Inclusion criteria 1 and 2 were amended to specify that subjects must be at least 18 years of age to participate in Study 200721, and subjects who participate in Study 200721 must also agree to participate in Study 200722, a separate infant follow-up study. Text was revised throughout to reflect the change in the subject age criterion and the requirement to enroll in the infant follow-up study. Section 9.2 was updated to clarify that the study would be conducted using the current version of the Declaration of Helsinki. Finally, an appendix was added that categorizes laboratory samples into those supporting study conduct and those that may be analyzed at a later date.		
2014N194185_02	2015-JAN-29	Country-Specific Protocol Amendment for Applicable UK Sites
The text from Section 5.3 has been clarified. The intent of the language remains the same, but the clarification confirms there is no requirement for the investigator to discuss unblinding with the PPD medical monitor in order to rapidly unblind treatment for a study subject if needed. In addition, Section 9.2 was updated to clarify that the study would be conducted using the current version of the Declaration of Helsinki.		
2014N194185_03	2015-FEB-04	Country-Specific Protocol Amendment for Applicable Swedish Sites
An appendix was added to list the medications considered strong, moderate, and weak CYP3A4 (cytochrome P450 3A4 enzyme) inhibitors and inducers.		
2014N194185_04	2016-AUG-22	Amendment No. 4
<p>The following changes are reflected in Protocol Amendment No. 4:</p> <ul style="list-style-type: none"> • 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 inclusion criteria for confirming sufficient dilation and effacement at Screening. • Clarify that co-morbid medical or obstetric conditions that may exclude a subject 		

from the study include known or suspected maternal Zika infection during gestation.

- Clarify the exclusion criterion for women with a history of substance abuse.
- Add an exclusion criterion for women for whom the combination of history and screening test results is suggestive of abuse or dependency.
- Clarify that withdrawal from the study will mean that no additional visits can occur or procedures performed.
- 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.
- Define inadequate treatment response.
- Clarify in the Time and Events Table the assessments performed at the face-to-face post-infusion visit and at the weekly telephone calls during the Post-Infusion Assessment Phase. Additionally, the optional retreatment visit was added to the table and the assessments that will be performed when a subject withdraws from the study were clarified.
- Add definitions for a completed subject and study completion.
- Update the atosiban preparation instructions.
- Add procedures that should be followed for managing dose interruptions.
- Clarify that there is no requirement for the investigator to discuss unblinding with the PPD medical monitor in order to rapidly unblind treatment for a study subject if needed.
- 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 presentation of the liver stopping criteria and add that for local laboratory results an isolated bilirubin $>1.5 \times$ the upper limit of normal is acceptable if bilirubin is fractionated and direct bilirubin is $<35\%$.
- 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 signs are assessed relative to dosing. Also, added an optional measurement of oxygen saturation at Screening only.
- Revise the timing of the pharmacokinetic (PK) sample taken at the onset of any maternal or fetal serious adverse event (SAE) from within 24 hours to within 12 hours after completion or discontinuation of investigational product.
- 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 and EuroQol 5-dimensional 5-level from ± 2 weeks to -2 weeks/+6 weeks.
- Add as a key secondary endpoint the PK analysis of retosiban clearance and volume of distribution and the effect of covariates on these parameters.
- Remove the listed exploratory endpoints and clarify that exploratory endpoints will be provided in the reporting and analysis plan.
- Remove the follow-up amniotic fluid index (AFI) by abdominal ultrasound as a fetal safety endpoint.
- Remove from the list of disease-related maternal and neonatal events those events that are already listed as adverse events (AEs) of special interest.
- Clarify the time period and frequency of reporting AEs and SAEs.
- Update the contact information for reporting SAEs.
- Add information for the follow-up of AEs and SAEs.
- 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.
- Remove the requirement for an ultrasound for determination of the AFI within 12 hours of completion of study treatment.
- Revise the method used for adjusting multiplicity of the key secondary endpoints from a stepwise Holm's test to a sequential testing method.
- Add an appendix that provides guidelines for reporting maternal, fetal, and neonatal AEs of special interest.
- Incorporate the changes detailed in the country-specific amendment for sites in France (dated 29 Jan 2015).
- Incorporate the changes detailed in the country-specific amendment for sites in the United Kingdom (dated 29 Jan 2015).
- Incorporate the changes detailed in the country-specific amendment for sites in Sweden (dated 04 Feb 2015).
- Incorporate other administrative changes.

2014N194185_05

2016-DEC-21

Amendment No. 5

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

- Remove the 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 or before retreatment unless the most recent ultrasound is within 3 weeks (21 days) before the date of randomization or the date of retreatment.
- Update the list of maternal drug-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.
- Remove changes detailed in the country-specific amendment for sites in France (dated 29 Jan 2015).
- Incorporate other administrative changes.

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21 Dec 2016
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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 200721 (ZINN)

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	

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LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AE	adverse event
AFI	amniotic fluid index
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4 enzyme
DRE	disease-related event
ECG	electrocardiogram
eCRF	electronic case report form
EDD	estimated date of delivery
EMA	European Medicines Agency
EPDS	Edinburgh Postnatal Depression Scale
EQ-5D-5L	EuroQol 5-dimensional 5-level
EQ VAS	EuroQol visual analogue scale
EUROCAT	European Surveillance of Congenital Anomalies
fFN	fetal fibronectin
GA	gestational age
GBS	group B streptococcal
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
IB	investigator's brochure
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
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
MACDP	Metropolitan Atlanta Congenital Defects Program
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
msec	millisecond

NaCl	sodium chloride
ng	nanogram
NICU	neonatal intensive care unit
pg	picogram
P-gp	P-glycoprotein
PK	pharmacokinetic
PPROM	preterm premature rupture of membranes
QTcF	corrected QT interval using Fridericia formula
RAP	reporting and analysis plan
RCOG	Royal College of Obstetricians and Gynecologists
RDS	respiratory distress syndrome
SAE	serious adverse event
SmPC	summary of product characteristics
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 <i>in vitro</i> fertilization or intrauterine insemination or (2) a best estimated due date confirmed or established by the earliest ultrasound performed prior to 24 ^{0/7} weeks' gestation
Postmenstrual age	Determined by adding chronological age to gestational age at delivery

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PROTOCOL SUMMARY

Rationale

Mortality and morbidity in premature infants are inversely proportional to gestational age (GA) at birth; babies born before 32^{0/7} weeks' gestation have the greatest risk for death and poor health outcomes [Saigal, 2008]. The inverse relationship between neonatal mortality and morbidity and 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. Tocolytic therapy is recommended for short-term delay of delivery in order to administer antenatal corticosteroids, but there is no evidence that current tocolytic regimens improve neonatal or infant outcomes beyond the effect of antenatal corticosteroids [Sanchez-Ramos, 1999; RCOG, 2011; ACOG, 2012; Roos, 2013]. Unfortunately, neonatal mortality and morbidity remain disproportionately high for this study population despite antenatal corticosteroids and highlight a critical need for new therapies to prolong pregnancy and improve neonatal outcomes.

Results from the OTA105256 Phase II 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, and this difference was consistent across GAs. The emerging safety profile for retosiban also appears favorable. All reported adverse events (AEs) (maternal, fetal, and neonatal) were generally consistent with either those reported in the investigator's brochure (IB) or in the population under study. A summary of the complete results for Study OTA105256 is included in the IB [GlaxoSmithKline Document Number CM2006/00201/05].

No placebo-controlled tocolytic studies have demonstrated an effect of this magnitude in spontaneous preterm labor. There is general agreement 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. This study (ZINN) is designed to test this hypothesis through a direct comparison with atosiban, a mixed oxytocin-vasopressin antagonist indicated for short-term use to delay imminent preterm birth in women between 24^{0/7} and 33^{6/7} weeks' gestation in preterm labor.

Objectives

The primary objective is to demonstrate the superiority of retosiban to prolong pregnancy compared with atosiban.

The following are the secondary objectives:

- To describe the outcomes of newborns during the neonatal period (through 28 days post estimated date of delivery [EDD]) for retosiban compared with atosiban
- To describe the maternal, fetal, and neonatal safety profile during and after intravenous (IV) retosiban treatment compared with atosiban treatment

- To determine the effect of retosiban treatment compared with atosiban on health care resource use and patient-reported outcomes associated with the maternal and neonatal hospitalization
- 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

The following are the exploratory objectives:

- To examine the relationship between the baseline fetal fibronectin value, cervical length, and other biomarkers and the response to any study treatment
- To examine the relationship between subclinical intrauterine infection and response to any study treatment
- To investigate the relationship between genetic variants in the mother and/or fetus either with the development or progression of preterm labor or other medically related conditions or with treatment response to any study treatment and concomitant medications, if indicated

Study Design

ZINN is a Phase III, randomized, double-blind, double-dummy, multicenter study. Approximately 330 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, will be randomly assigned to retosiban or atosiban in a 1:1 ratio.

- **Test Treatment: Retosiban**

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 subjects with an inadequate response any time after the first hour of treatment, investigators should increase the dose by another 6-mg IV loading dose and increase the infusion rate to 12 mg/hour for the remainder of the 48-hour treatment period (for details see [Table 3](#)).

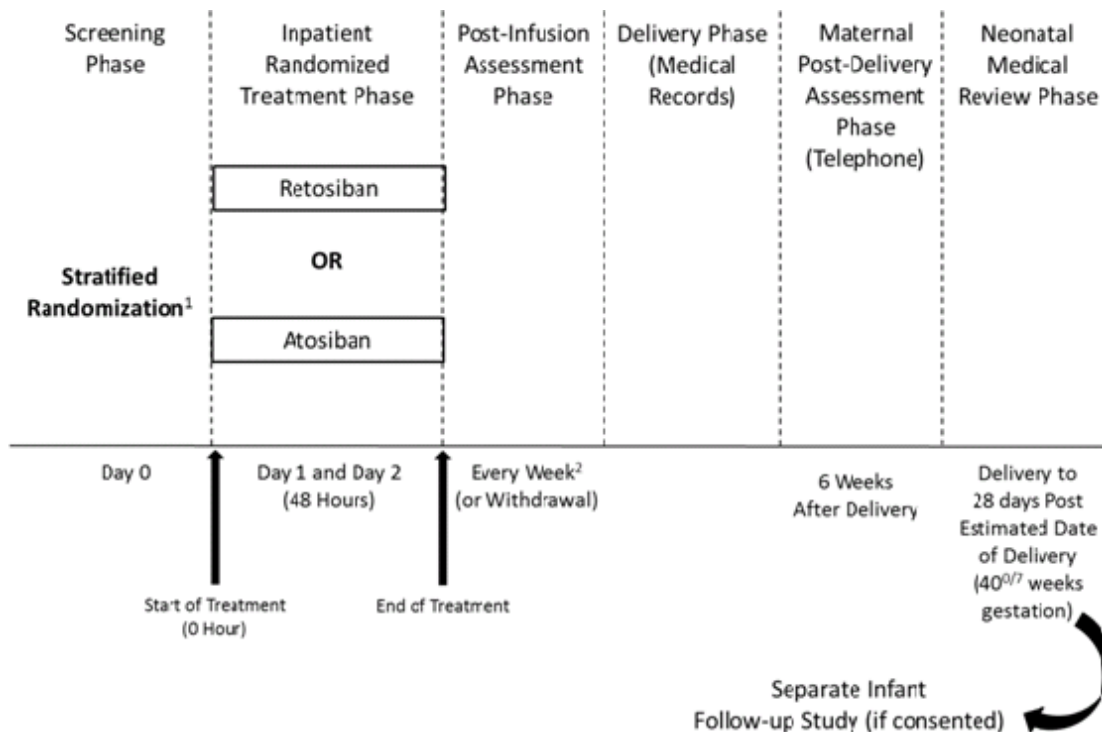
- **Active Control: Atosiban**

Atosiban will be administered in 3 successive stages: an initial bolus dose (6.75 mg) over 1 minute, immediately followed by a continuous infusion at 18 mg/hour for 3 hours, followed by a 6-mg/hour infusion for the remainder of the 48-hour treatment period (for details see [Table 4](#)).

For undelivered subjects who are subsequently diagnosed with recurrent preterm labor following the Inpatient Randomized Treatment Phase, retreatment with blinded investigational product (IP) is permitted. Retreatment is limited to a single repeat course of the blinded IP to which the subject was originally randomly assigned, either retosiban or atosiban. Retreatment is only permitted if the subject presents prior to 33^{6/7} weeks' gestation and meets the criteria specified in the Time and Events Table.

ZINN will consist of 6 phases: Screening, Inpatient Randomized Treatment, Post-Infusion Assessment, Delivery, Maternal Post-Delivery Assessment, and Neonatal

Medical Review (see schematic). The duration of any 1 subject's (maternal or neonatal) participation in the study will be variable and dependent on GA at study entry and the date of delivery.



1. Stratification (1:1) to retosiban or atosiban 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. Subjects who have not delivered after 48 hours will return for a face-to-face post-infusion assessment 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 atosiban) is allowed.

Prior to randomization, each subject will be stratified by progesterone treatment and GA 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 prior to 24^{0/7} weeks' gestation. 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}.

The Screening Phase will occur on Day 0 and assessments will primarily focus on maternal and fetal safety evaluations prior to dosing. 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 managed per the investigator's judgment.

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 assessment visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase (Note: study documents may reference this visit as the 1-week face-to-face post-infusion assessment visit). The subject will then be contacted every week via telephone to determine if birth has occurred. If the subject delivers the baby prior to the face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and liver function tests (see [Table 5](#)) and the assessments for the Delivery Phase (see [Section 3.1.4](#)) will be performed.

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. During the Maternal Post-Delivery Assessment Phase, the subject will be contacted by telephone within 6 weeks of delivery for a post-delivery assessment.

During the Neonatal Medical Review Phase, the neonatologist subinvestigator will conduct a comprehensive review of the newborn's medical records, including any admission to an intensive or specialized care unit and any hospital readmission or outpatient surgery, from delivery through 28 days EDD, where EDD is defined as 40^{0/7} weeks' gestation for all subjects.

The subject or other legal guardian for the infant will also be asked to consent to participate in a separate 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 face-to-face post-infusion assessment visit.

An interim analysis will occur after approximately 130 subjects have completed delivery and have time-to-delivery results available. At the interim analysis, all available safety and efficacy data will be reviewed by an unblinded independent data monitoring committee who may make recommendations to terminate the study.

Study Endpoints/Assessments

The primary efficacy endpoint is time to delivery from the start of IP administration until delivery, based on a records review.

The following are the key secondary efficacy endpoints:

- 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
- Proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite determined up to 28 days after EDD (of $40^{0/7}$ weeks) (details for each composite are provided in Section 6.2.4)
 - Fetal or neonatal death
 - Respiratory distress syndrome (RDS)
 - Bronchopulmonary dysplasia
 - Necrotizing enterocolitis or isolated perforation
 - Sepsis
 - Meningitis
 - Retinopathy of prematurity
 - Intraventricular hemorrhage (IVH)
 - White matter injury
 - Cerebellar hemorrhage
- Retosiban clearance and volume of distribution and the effect of covariates on these parameters

The following are other secondary efficacy endpoints:

- Proportion of neonates with any of the 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
- Proportion of births prior to $28^{0/7}$ weeks' gestation
- Proportion of births prior to $32^{0/7}$ weeks' gestation
- Proportion of births ≤ 7 days
- Proportion of births ≤ 48 hours
- Proportion of births ≤ 24 hours

The following are the safety endpoints (maternal, fetal, and neonatal, as appropriate):

- Incidence of reported AEs and serious AEs
- Significant changes in vital signs and clinical laboratory tests

- Incidence of treatment-limiting toxicities including both clinical and laboratory etiology causing subject to discontinue study treatment
- Edinburgh Postnatal Depression Scale
- Fetal acidosis
- Neonatal Apgar scores (at 1 and 5 minutes after birth), growth parameters (weight, length, and head circumference) at birth and at discharge, and documentation of any complications
- AEs of special interest
 - Maternal
 - Death
 - Chorioamnionitis and its complications
 - Placental abruption
 - Postpartum hemorrhage and/or retained placenta
 - Pulmonary edema
 - Fetal
 - Intrauterine fetal demise
 - Category II or III fetal heart rate tracing (defined according to American College of Obstetricians and Gynecologists Practice Bulletin 106 [[ACOG](#), 2009])
 - Fetal inflammatory response syndrome
 - Neonatal
 - 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

1. INTRODUCTION

1.1. 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, 2011; ACOG, 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, 2010; ACOG, 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. Retosiban is under development as a solution for intravenous (IV) infusion for the treatment of spontaneous preterm labor in women with intact membranes. This study is being conducted to demonstrate the superiority of retosiban in prolonging pregnancy compared with atosiban, a mixed oxytocin and vasopressin antagonist that is a European Medicines Agency (EMA)-approved treatment of preterm labor in all member states of the European Union.

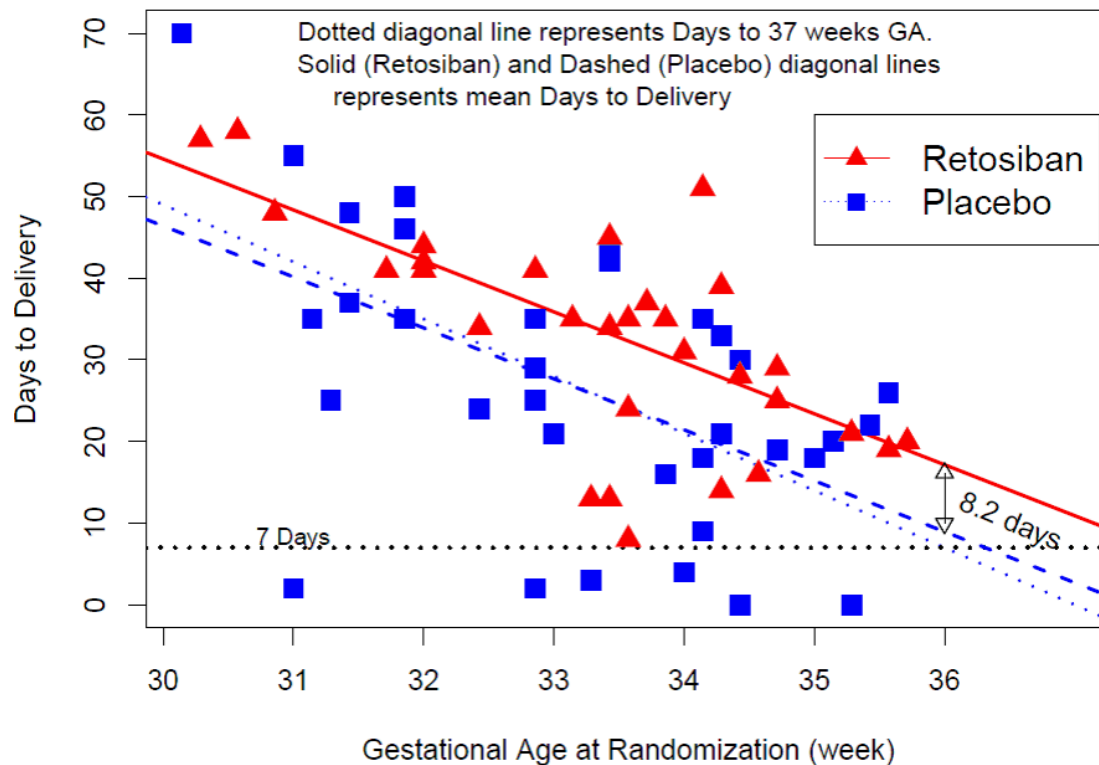
1.2. Rationale

This study is being conducted based on the results of the OTA10256 study that demonstrated significantly longer time to delivery. Specifically, OTA105256 was a Phase II study of retosiban for the treatment of spontaneous preterm labor in women with singleton pregnancies and intact membranes. This study initially examined the pharmacokinetics, dose response, and safety of retosiban in women for whom the gestational age (GA) was restricted to 34^{0/7} and 35^{6/7} weeks. Retosiban was given intravenously with the loading dose and infusion rate increased in a stepwise fashion every 3 hours to achieve target plasma concentrations. Alternate tocolytic drugs were not permitted during the study's IV infusion phase. Twenty-nine adult subjects (ages 18 to 37 years) were enrolled into Parts A and B. An interim analysis, indicating retosiban suppressed contractions and prolonged pregnancy, resulted in an additional cohort (Part C with a lowered GA to 30^{0/7} weeks) to evaluate retosiban in a clinical population and setting more consistent with current practice guidelines for tocolytic use. Sixty-four adult subjects (ages 18 to 41 years) were enrolled, randomly assigned to treatment, and dosed in Part C.

Data from Study OTA105256 found that retosiban treatment, at a dosing regimen of 6-mg load over 5 minutes, then 6 to 12 mg/hour based on response, was associated with a higher proportion of females achieving uterine quiescence and a significant difference in time to delivery and reduction in preterm births. Uterine quiescence was defined as 4 or fewer contractions per hour with no change in cervical dilation greater than 1 cm. Using partial informative priors, which partially weighted the Part A/B response rates for retosiban and placebo, the posterior mean response rate within the initial 6 hours of treatment was 62% in the retosiban group compared with 41% in the placebo group. The posterior relative risk of achieving quiescence was 1.53 (95% confidence interval [CI]: 0.98, 2.48).

Retosiban treatment was also associated with a significant difference in time to delivery and births prior to 37 weeks of gestation. The posterior mean difference in time to delivery was 8.2 days relative to placebo (95% CI: 2.7, 13.74). The percent of preterm births in the retosiban and placebo groups was 18.7% and 47.2%, respectively. The posterior relative risk for preterm birth in the retosiban group was 0.38 (95% CI: 0.15, 0.81).

A comparison of the retosiban and placebo treatment groups for the difference in time to delivery is shown in [Figure 1](#).

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 consistent with either those reported in the investigator's brochure (IB) or in the population under study. A summary of the complete results for Study OTA105256 is included in the IB [GlaxoSmithKline Document Number [CM2006/00201/05](#)].

No placebo-controlled tocolytic studies have demonstrated an effect of this magnitude in spontaneous preterm labor. There is general agreement 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. This study (ZINN) is designed to test this hypothesis through a direct comparison with atosiban, a mixed oxytocin vasopressin antagonist indicated for short-term use to delay imminent preterm birth in women between 24^{0/7} and 33^{6/7} weeks' gestation in preterm labor.

1.3. Benefit:Risk Assessment

Summaries of findings from both clinical and nonclinical studies conducted with GSK221149 can be found in the IB [GlaxoSmithKline Document Number [CM2006/00201/05](#)]. [Table 1](#) and [Table 2](#) outline the risk assessment and mitigation strategy for this protocol.

1.3.1. Risk Assessment

Table 1 Potential Risks of Clinical Significance

Retosiban [e.g., GSK221149]		
Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Fetal exposure through placental transfer	<p>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.</p> <p>The preclinical data indicate very minimal, if any, maternal CNS penetration or placental transfer of retosiban as supported by:</p> <ul style="list-style-type: none"> 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. <p>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.</p> <p>The short half-life of retosiban (~2 hours) is expected to minimize any significant risk.</p>	<p>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.</p> <p>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.</p> <p>Unblinded safety data will be monitored by an IDMC.</p>

Retosiban [e.g., GSK221149]		
Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Neonatal exposure via breast milk	<p>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.</p> <p>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.</p>	<p>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.</p> <ul style="list-style-type: none"> 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. <p>Safety monitoring for signals indicating adverse effects in infants following exposure to retosiban via breastfeeding will be performed throughout the study.</p> <p>Unblinded safety data will be monitored by an IDMC, including infants exposed to retosiban via breastfeeding.</p>

Retosiban [e.g., GSK221149]		
Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Uterine atony and postpartum hemorrhage due to oxytocin receptor antagonism	<p>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.</p> <p>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.</p> <p>The available clinical data for other oxytocin antagonists suggest the adverse effects of atony and postpartum hemorrhage are limited [Valenzuela, 1995; Thornton, 2009].</p> <p>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.</p> <p>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:</p> <ul style="list-style-type: none"> 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. <p>The incidence of primary postpartum hemorrhage (within 24 hours of delivery) is estimated to be between 4% to 6% of mothers who delivered [ACOG, 2006].</p>	<p>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.</p> <p>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.</p> <p>Retained placenta and postpartum hemorrhage are AEs of special interest requiring the collection/assessment of risk factors for postpartum hemorrhage, eCRFs for any event of postpartum hemorrhage, and clinical parameters related to postpartum hemorrhage. Evaluations will include outcomes such as time from delivery to expulsion of placenta and estimated blood loss.</p> <p>Unblinded safety data will be monitored by an IDMC.</p>

Retosiban [e.g., GSK221149]		
Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
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].	<p>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.</p> <p>Placental tissue samples will be collected in this study (200721 [ZINN]) when delivery occurs at an investigative center to examine safety and efficacy outcomes in subjects with subclinical intrauterine infection.</p> <p>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 on 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.</p>
Potential drug-drug interaction with inhibitors of BCRP or P-gp	<p>Retosiban is a substrate of murine BCRP and P-gp <i>in vitro</i>. Inhibitors of BCRP and P-gp have the potential to increase exposure of retosiban when co-administered.</p> <p>BCRP and P-gp are 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.</p> <p>Clinical experience with exposures 10-fold higher than the exposure at the planned therapeutic dose have shown retosiban to be safe and well tolerated, with no observed untoward effects in adult women of childbearing potential.</p>	<p>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.</p> <p>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.</p>
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 C _{max} 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 5.1.1.1 and the IB). Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure.

Retosiban [e.g., GSK221149]		
Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
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 inducers concomitantly with IP requires an adjustment to the retosiban dosing regimen (see Section 5.1.1.1 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; CYP3A4 = cytochrome P450 3A4 enzyme; eCRF = electronic case report form; IB = investigator's brochure; IP = investigational product; IDMC = independent data monitoring committee; P-gp = P-glycoprotein.

Table 2 Potential Safety Concerns

Potential Safety Concerns	Summary of Data / Rationale for Concern	Mitigation Strategy
Pulmonary edema	<p>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.</p> <p>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].</p>	<p>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.</p> <p>Combination administration of a tocolytic is not permitted in the clinical studies.</p> <p>Maintenance tocolysis is not allowed.</p> <p>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.</p>

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

1.3.2. Benefit Assessment

An estimated 14.9 million babies were born prematurely in 2010, representing 11% of all live births worldwide [Blencowe, 2012]. Preterm birth rates ranged from about 5% in several European countries to 18% in some African countries. Babies born prematurely are at risk for death, short-term medical complications, long-term disabilities, and developmental problems; these risks are inversely related to GA. Although babies born before 32 weeks have the greatest risk for death and poor health outcomes [Saigal, 2008; Lundqvist, 2009; Mathews, 2010], late preterm infants (defined as 34^{0/7} to 36^{6/7} weeks) are now known to carry a higher risk of morbidity and mortality than term infants [Engle, 2007]. Approximately 40% to 45% of preterm births are preceded by spontaneous preterm labor; the remainder is associated with PPROM and clinical indications for delivery [Romero, 2000; Goldenberg, 2008].

Treatment of spontaneous preterm labor is aimed at improving outcomes for the child and should be considered in women for whom a delay in delivery will provide benefit to the newborn. Tocolytic therapy is currently recommended for short-term delay of delivery in order to administer antenatal corticosteroids, which reduce the risks for neonatal mortality and morbidity, and transfer the mother to a neonatal specialized care unit. However, there is no evidence that current tocolytic regimens improve neonatal or infant outcomes beyond the effect of antenatal corticosteroids [RCOG, 2011; ACOG, 2012; Roos, 2013].

Given the inverse relationship between the risks for prematurity complications and GA at birth, the development of a treatment that significantly prolongs pregnancy in subjects with preterm labor would be invaluable if associated with improved perinatal outcomes. Results from the Phase II study OTA105256 offer hope that retosiban may prolong pregnancy to such a degree that perinatal outcomes could be favorably affected.

Retosiban is highly selective for the oxytocin receptor. Significant toxicity to major end-organ systems has not been detected in preclinical or clinical testing to date. These findings indicate the risk for adverse effects related to off-target receptor binding is low. Maternal and fetal exposure will be limited to 48 hours, and exposure occurs after fetal organogenesis is complete.

The active control in the study, atosiban, is a mixed oxytocin and vasopressin antagonist that is an EMA-approved drug marketed in the European Union since 2000. Atosiban is indicated to delay imminent preterm birth in pregnant adult women. No benefit to the neonate has been demonstrated in clinical trials using atosiban [Tractocile SmPC, 2013]. Subjects randomly assigned to this treatment group, therefore, will have the opportunity for a treatment benefit that will prolong pregnancy sufficiently to allow for antenatal corticosteroid treatment. The label indicates adverse reactions are generally mild, with nausea as the most commonly reported adverse maternal effect. Moreover, clinical trials did not reveal any specific adverse neonatal effects and long-term effects in the infant were in the range of normal variation and comparable with both placebo and β -agonists' rates.

1.3.3. Overall Benefit:Risk Conclusion

Despite the proven benefit of antenatal corticosteroids, neonatal mortality and morbidity remain disproportionately high in the study population. The Phase II program found that retosiban treatment significantly increased the time to delivery and reduced preterm births. These findings suggest the potential for retosiban to provide additional benefit by allowing for continued maturation of fetal organs and systems.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with retosiban and atosiban are justified by the anticipated benefits that may be afforded to subjects with preterm labor.

The overall benefit:risk assessment of retosiban appears favorable 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 [GlaxoSmithKline Document Number [CM2006/00201/05](#)].

2. OBJECTIVES

2.1. Primary Objective

- To demonstrate the superiority of retosiban to prolong pregnancy compared with atosiban

2.2. Secondary Objectives

- To describe the outcomes of newborns during the neonatal period (through 28 days post estimated date of delivery [EDD]) for retosiban compared with atosiban
- To describe the maternal, fetal, and neonatal safety profile during and after IV retosiban treatment compared with atosiban treatment
- To determine the effect of retosiban treatment compared with atosiban on health care resource use and patient-reported outcomes associated with the maternal and neonatal hospitalization
- 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

2.3. Exploratory Objectives

- To examine the relationship between the baseline fetal fibronectin (fFN) value, cervical length, and other biomarkers and the response to any study treatment
- To examine the relationship between subclinical intrauterine infection and response to any study treatment

- To investigate the relationship between genetic variants in the mother and/or fetus either with the development or progression of preterm labor or other medically related conditions or with treatment response to any study treatment and concomitant medications, if indicated

3. INVESTIGATIONAL PLAN

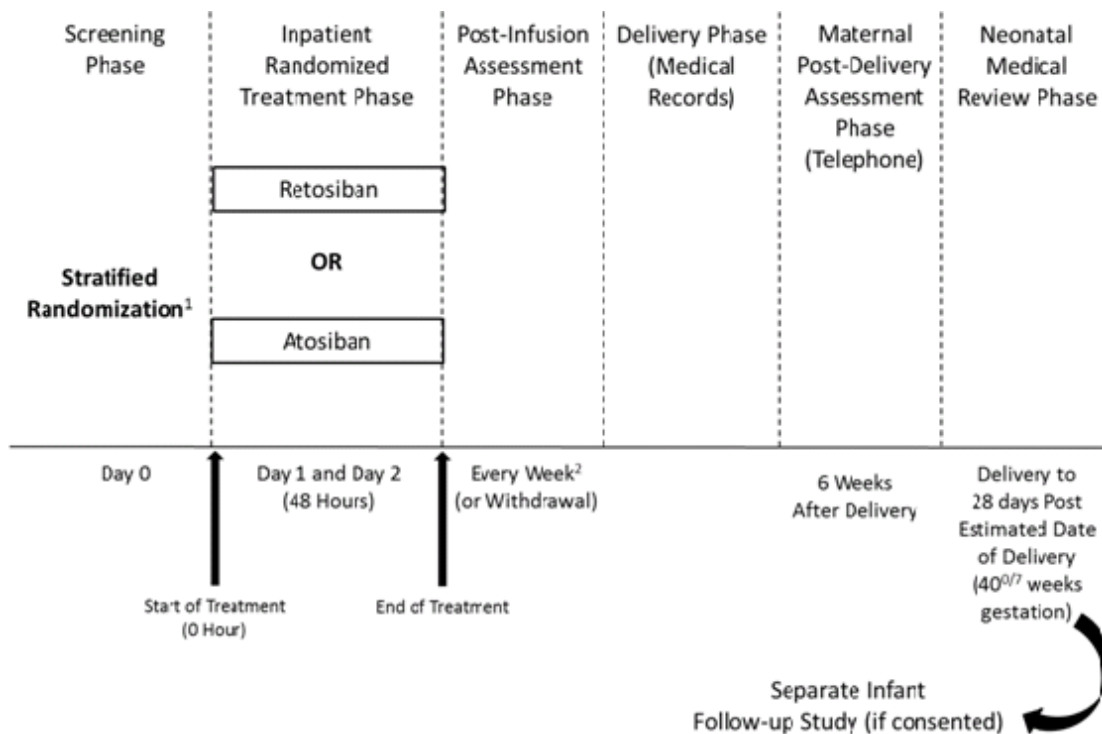
3.1. Study Design

ZINN is a Phase III, randomized, double-blind, double-dummy, multicenter study. This study will be conducted in approximately 330 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 1:1 to receive either retosiban IV infusion over 48 hours or atosiban IV infusion over 48 hours.

Each investigational site will have an obstetrician with expertise in maternal-fetal medicine as the principal investigator who will be responsible for treatment, care, and review of data for the mother during the 6 phases of the study and a neonatologist as a subinvestigator who will review the newborn hospital records to track and record the neonatal information, as required by the study protocol. The specific responsibilities of the obstetrician investigator and the neonatologist subinvestigator are outlined in the Study Procedures Manual (SPM).

Prior to randomization, each subject will be stratified by progesterone treatment and GA 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 prior to 24^{0/7} weeks' gestation. 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}.

ZINN will consist of 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 atosiban 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. Subjects who have not delivered after 48 hours will return for a face-to-face post-infusion assessment 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 atosiban) is allowed.

The Screening Phase will occur on Day 0 and assessments and will primarily focus on maternal and fetal safety evaluations prior to dosing. 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 managed per the investigator's judgment. Subjects who remain undelivered after 48 hours will be scheduled for a face-to-face post-infusion assessment visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase (Note: study documents may reference this visit as the 1-week face-to-face post-infusion assessment visit). The subject will then be contacted every week via telephone to determine if birth has occurred. If the subject delivers the baby prior to the face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and liver function tests (see [Table 5](#)) and the assessments for the Delivery Phase (see [Section 3.1.4](#)) will be performed.

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. For those subjects who deliver at the investigative center, a placental tissue sample will be obtained at the time of delivery for central histopathology examination and a cord blood sample will be collected for potential genetic research and biomarker assays. If delivery occurs within 12 hours of investigational product (IP) (retosiban or atosiban) completion or discontinuation, the cord blood sample will also be used for the pharmacokinetic (PK) assessment, and, if required, a corresponding maternal blood sample will be collected for PK analysis (see Section 6.5.1). 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. A maternal post-delivery assessment will be conducted by telephone within 6 weeks of delivery.

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) and the EQ-5D-5L (-2 weeks/+6 weeks).

During the Neonatal Medical Review Phase, the neonatologist subinvestigator will conduct a comprehensive review of the newborn's medical records, including any admission to an intensive or specialized care unit and any hospital readmission or outpatient surgery, from delivery through 28 days EDD, where EDD is defined as 40^{0/7} weeks' gestation for all subjects.

The subject or other legal guardian for the infant will also be asked to consent to participate in a separate 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 face-to-face post-infusion assessment visit.

An interim analysis will occur after approximately 130 subjects have completed delivery and have time-to-delivery results available. At the interim analysis, all available safety and efficacy data will be reviewed by an unblinded independent data monitoring committee (IDMC) who may make recommendations to terminate the study (see Section 9.8). Details of the interim analysis are provided in Section 8.3.4. Subjects will continue to be enrolled while the interim analysis is being conducted.

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 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 (for details see Table 3). Investigators will be required to indicate in the electronic case report form (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

response. The duration of the treatment should not exceed 48 hours and the total dose should not exceed 582 mg.

Atosiban will be given intravenously in 3 successive stages: an initial bolus dose of 6.75 mg using atosiban 6.75-mg/0.9-mL solution for injection, immediately followed by a continuous high-dose infusion at 18 mg/hour for 3 hours, then a lower 6-mg/hour infusion for the remainder of the 48-hour treatment period using the atosiban 37.5 mg/5-mL concentrate for solution. The duration of the treatment should not exceed 48 hours and the total dose should not exceed 330 mg.

A single repeat episode of IP treatment may be used if a subject experiences another episode of preterm labor 24 hours or more following completion of the Inpatient Randomized Treatment Phase, as long as the subject still meets all eligibility criteria (see Section 3.1.3.1).

Antenatal corticosteroid treatment should be administered in accordance with national, society, or institutional guidelines. Investigators should also follow national, society, or institutional guidelines for the use of magnesium sulfate for fetal neuroprotection. Antibiotic treatment for group B streptococcal infections (GBS) is allowed per institutional guidelines.

Randomized treatment can be discontinued as outlined in Section 4.4.2. Subjects discontinuing randomized treatment will be managed according to the standard care and asked to remain on study through the Maternal Post-Delivery Assessment Phase. These subjects will also be asked to consent to the infant follow-up study.

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

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM will provide the site staff with administrative and detailed technical information that does not impact subject safety.

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 (Table 5), are essential and required for study conduct.

3.1.1. Screening Phase

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 sign measurements, cervical examination, medical and obstetric history, estimated GA). However, 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 the consent having been signed.

Institutions that routinely perform 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 (see Section 6.7). Likewise, institutions that routinely measure cervical length by transvaginal ultrasound should record the result in the eCRF. Cervical length data will not be used to determine subject eligibility but will be used in an exploratory analysis (see Section 6.6).

The GA will be 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 prior to 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.

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 assessments must include a formal review of medical and obstetric history and a review of all eligibility requirements for the study. Cardiovascular medical history/risk factors will also be assessed. Concomitant medications will be reviewed and the investigator will attempt to obtain a complete history of any medications taken during the pregnancy (including trimester of exposure if possible). Monitoring for both maternal and fetal AEs will begin.

Additional screening assessments are described in Table 5.

Eligible subjects will be randomly assigned to treatment (see Section 5.3). At randomization, the fetus will be issued a separate subject number for tracking of efficacy and safety assessments.

3.1.2. Inpatient Randomized Treatment Phase

3.1.2.1. Before Treatment

Prior to dosing, the investigators must confirm the fetal heart rate pattern remains reassuring, that, according to medical discretion, tocolytic therapy is still indicated, and the electrocardiogram (ECG) does not have clinically significant abnormalities (see Section 6.1).

3.1.2.2. During Treatment

Assessments performed during the treatment period are described in Table 5.

Antenatal corticosteroid treatment should be administered in accordance with national, society, or institutional guidelines. Investigators should also follow national, society, or institutional guidelines for the use of magnesium sulfate for fetal neuroprotection. Antibiotic treatment for GBS infections is also allowed per institutional guidelines.

Progesterone may be continued for subjects already on established progesterone therapy

but should not be initiated in a subject after she has been enrolled in the study.

3.1.2.3. End of Treatment

An end-of-treatment examination will be conducted after the subject has completed the infusion and before she is released from the acute care setting (either to a nonacute care setting or to home).

The subject or other legal guardian for the infant (both delivered and undelivered) will be asked to consent to participate in a separate long-term infant follow-up study for safety and neurodevelopment, if not already obtained.

The study site staff will schedule the face-to-face post-infusion assessment visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) after the end of treatment (see Section 3.1.3).

If the subject delivers the baby prior to the face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and liver function tests (see Table 5) and the assessments in Section 3.1.4 will be performed.

3.1.3. Post-Infusion Assessment Phase

Subjects who remain undelivered after 48 hours will be scheduled for a face-to-face post-infusion assessment 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. See Section 3.1.2.3 for details on required assessments when the baby is delivered before the face-to-face post-infusion assessment visit.

The subject will then be contacted every week via telephone to determine if she has delivered (see Section 3.1.4 for a summary of assessments performed at delivery). Note: This assessment should be completed remotely (by telephone); however, 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 a telephone assessment is due, this assessment may be completed face-to-face.

3.1.3.1. Retreatment

For undelivered subjects who are subsequently diagnosed with recurrent preterm labor 24 hours or more following completion of the Inpatient Randomized Treatment Phase, retreatment with blinded IP is permitted at the discretion of the investigator. Retreatment is limited to a single repeat course of the blinded IP to which the subject was originally randomly assigned, either retosiban or atosiban. Retreatment is only permitted if the subject experiences a spontaneous preterm labor recurrence before 33^{6/7} weeks' gestation and meets the criteria specified in the Time and Events Table (Table 5). Atosiban retreatment guidelines are provided in the summary of product characteristics (SmPC) [Tractocile SmPC, 2013].

The requirement for a repeat course of antenatal corticosteroid therapy should be determined in accordance with national, society, or institutional guidelines (e.g., [RCOG, 2010; ACOG, 2011]). Investigators should also follow national, society, or institutional guidelines for the use of magnesium sulfate for fetal neuroprotection. Antibiotic treatment for GBS is also allowed per institutional guidelines.

3.1.4. Delivery Phase

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. These procedures include identification at conclusion of Inpatient Randomized Treatment Phase of the intended delivery caregiver, ensuring the delivery caregiver or neonatal intensive care unit (NICU) staff understand the information needed for the study, those events that require rapid communication to clinical investigators, and a process that ensures clinical investigators can contact the appropriate personnel in case of follow-up questions.

For subjects who deliver at the investigative center, a placental tissue sample will be obtained at the time of delivery for central histopathologic examination and a cord blood sample will be collected for potential genetic research and biomarker assays. If delivery occurs within 12 hours of IP completion or discontinuation, the cord blood sample will also be used for the PK assessment (see SPM for information about how these samples will be collected), and, if required, a corresponding maternal blood sample will be collected for PK analysis (see Section 6.5.1). In addition, 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 (see Section 6.5.3).

The following information regarding the delivery and hospitalization for mother and newborn will be obtained through a review of the hospital records:

- Date and time of delivery
- Mode of delivery
- Indication for delivery
- Concomitant medications
- Maternal AEs and serious AEs (SAEs) (including AEs of special interest; Section 6.3.2.3)
- Maternal health care resource use

The newborn medical records will also be reviewed in order to record the following:

- Variables relevant to the composite
- Apgar scores at 1 and 5 minutes
- Length, weight, and head circumference
- Blood gases (when available)

- Hospital length of stay
- Neonatal health care resource use
- Neonatal AEs and SAEs; in particular, the review will focus on any complications requiring intensive or specialized care and information specific to complications of prematurity will be collected (see Section 6.3.2 and Section 6.3.7.2).

3.1.5. Maternal Post-Delivery Assessment Phase

The subject will be contacted via telephone for the Maternal Post-Delivery Assessment Phase to be conducted within 6 weeks following delivery. Maternal assessments conducted at this contact will include the following:

- Review of concomitant medications and medical/obstetric history (± 2 weeks)
- Recording of AEs and SAEs (maternal) (± 2 weeks)
- Recording of AEs and SAEs of neonate if discharged from hospital and through 28 days post EDD (± 2 weeks)
- Status of breastfeeding (± 2 weeks)
- Postnatal administration of the Edinburgh Postnatal Depression Scale (EPDS) and the EuroQol 5-dimensional 5-level (EQ-5D-5L) questionnaire (-2 weeks/+6 weeks)
- Assessment of postpartum bleeding (± 2 weeks)

The subject or other legal guardian will be asked to provide consent for the infant (whether delivered or undelivered) to participate in a separate infant follow-up study for safety and neurodevelopment, if not already obtained.

3.1.6. Neonatal Medical Record Review Phase

Newborns will be followed in this study through 28 days post EDD as outlined in Table 5. 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.

3.2. Discussion of Design

3.2.1. Study Treatments

3.2.1.1. 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 treatment 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, 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 (for details see [Table 3](#)).

The retosiban dosing regimen has been informed by animal studies defining retosiban concentrations for inhibition of myometrial contractions, evaluations of exposure, safety, and tolerability over a wide range of doses in healthy subjects, and forced titration studies in pregnant women. The retosiban regimen is designed to yield a mean steady-state concentration of 75 ng/mL. The option to double the dose after 1 hour allows for between-subject variability in retosiban pharmacokinetics, receptor density, and 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 the Phase III dosing regimen will likely yield steady-state concentrations in the range of 50 to 388 ng/mL 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 (see IB [GlaxoSmithKline Document Number [CM2006/00201/05](#)]).

Retosiban is primarily metabolized by the cytochrome P450 (CYP) 3A4 enzyme (CYP3A4). Drug-drug interaction studies indicate retosiban exposure is increased approximately 9-fold during co-administration of the potent CYP3A4 inhibitor ketoconazole, whereas concomitant administration of the potent CYP3A4 inducer efavirenz decreased retosiban exposure 30%. As a result, the retosiban dosing regimen requires adjustment in subjects treated concomitantly with drugs that are potent CYP3A4 inhibitors or CYP3A4 inducers in order to achieve therapeutic retosiban concentrations. Refer to Section [5.1.1](#) for a description of the adjustments to the retosiban loading dose and infusion rate during co-administration with potent CYP3A4 inhibitors or CYP3A4 inducers.

3.2.1.2. Active Control

The active control in this study is atosiban, which is a mixed oxytocin/vasopressin antagonist approved in the European Union for short-term delay of imminent preterm birth in pregnant adult women in preterm labor. Atosiban was chosen as the active control because it represents a standard care tocolytic treatment aimed at delaying delivery in the targeted study population for at least 48 hours in order to complete antenatal corticosteroid treatment (using betamethasone or dexamethasone) and transfer of the mother to a specialized care unit [[Di Renzo, 2006b](#); [RCOG, 2011](#)]. No current evidence indicates that atosiban provides neonatal benefit beyond that of antenatal corticosteroids; therefore, the superiority study design will allow for demonstrating the

superiority of retosiban compared with atosiban for prolonging pregnancy and improving neonatal outcomes.

Atosiban will be administered to a study population and using a dosing regimen in accordance with the approved label. Atosiban is administered intravenously as a 6.75-mg bolus dose, followed by an 18-mg/hour continuous infusion for 3 hours, after which the continuous infusion rate is decreased to 6 mg/hour for the remainder of the 48-hour treatment period. The maximum atosiban dose is 330 mg, and the duration of the treatment should not exceed 48 hours [[Tractocile](#) SmPC, 2013].

Of note, the different infusion rates for retosiban and atosiban require a double-dummy technique in order to maintain blinding (see Section [5.4](#)).

3.2.1.3. Corticosteroids and Magnesium Sulfate

Antenatal corticosteroids are associated with a significant reduction in rates for respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and neonatal death. As a result, practice guidelines recommend a single course of corticosteroids for all pregnant women between 24 and 34 weeks' gestation who are at risk of preterm delivery within 7 days [[Di Renzo](#), 2006a; [RCOG](#), 2010; [ACOG](#), 2012]. In this study, antenatal corticosteroid treatment should be administered in accordance with national, society, or institutional guidelines.

Practice guidelines for the use of magnesium sulfate for fetal neuroprotection have been developed by the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice and Society for Maternal Fetal Medicine [[ACOG](#), 2010], the Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel [[Antenatal](#) Magnesium Sulphate for Neuroprotection Guideline Development Panel, 2010], and the Society of Obstetricians and Gynaecologists of Canada [[SOGC](#), 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 should administer magnesium sulfate for fetal neuroprotection according to national, society, or institutional guidelines [[ACOG](#), 2010; [Antenatal](#) Magnesium Sulphate for Neuroprotection Guideline Development Panel, 2010; [SOGC](#), 2011].

3.2.2. Study Population

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. Preterm birth rates range from approximately 5% in several European countries to 18% in some African countries. Birth prior to 34 weeks' gestation represents roughly 30% of preterm births in the United States, half of which are preceded by spontaneous labor [[Tucker](#), 1991; [Berkowitz](#), 1998; [Meis](#), 1998; [Goldenberg](#), 2008; [Martin](#), 2012;]. Premature birth in this group carries a disproportionately high risk for death, neonatal complications, and long-term disabilities. The vulnerability of this group for poor infant outcomes forms the basis for treatment guidelines aimed at improving neonatal and infant outcomes. These include antenatal corticosteroids, short-term tocolysis to complete antenatal corticosteroid treatment, and magnesium sulfate for fetal neuroprotection.

Pregnant adolescents aged 12 to 17 years are included based on prior discussions with regulatory agencies, unless national or local regulations restrict the age for study enrollment to subjects 18 to 45 years (see Section 4.2). 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]. The safety and efficacy of atosiban in pregnant women aged less than 18 years have not been established [Tractocile SmPC, 2013].

Clinical criteria for the diagnosis of preterm labor is generally based on the presence of either regular uterine contractions accompanied by a change in cervical dilation and/or effacement or initial presentation of regular contractions and cervical dilation of at least 2 cm [ACOG, 2012]. Dilation criteria for published studies in a preterm labor population generally included contraction criteria and cervical dilation ranging from 0 to 4 cm. Based on discussions with maternal fetal medicine specialists, spontaneous preterm labor will be based on regular uterine contractions at a rate of ≥ 4 contractions of at least 30 seconds duration during a 30-minute interval (confirmed by tocodynamometry) and at least one of the following: cervical dilation ≥ 2 cm and ≤ 4 cm by digital cervical examination or if < 2 cm dilation by digital cervical examination, a cervical change consisting of an increase of at least 25% effacement or 1 cm dilation.

Subject selection criteria were developed in consultation with maternal-fetal medicine specialists and are consistent with practice guidelines advising that tocolysis should not be used where there is a contraindication to prolonging pregnancy. These include pregnancies with known lethal congenital or chromosomal malformation, intrauterine infection, severe pre-eclampsia or eclampsia, placental abruption, advanced cervical dilation, and evidence of fetal compromise or placental insufficiency [RCOG, 2011; ACOG, 2012]. Women with comorbid medical or obstetric conditions that, in the opinion of the investigator, have the potential to complicate the pregnancy course and outcomes or predispose the subject to SAEs are also excluded from the study (see Section 4.3).

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Approximately 330 women (165 per treatment group) will be randomly assigned to ensure that approximately 300 women/newborns have recorded birth data (assumes 10% missing data).

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK IP or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number CM2006/00201/05], the package insert for atosiban [Tractocile SmPC, 2013], and other pertinent documents.

Deviations from inclusion 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.

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Signed and dated written informed consent is required prior to a subject's participation in Study 200721 (ZINN) 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: 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.)
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 prior to 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
 - A 1-cm increase in cervical dilation by digital cervical examination
5. Treatment-naïve subjects and subjects not adequately responding to tocolytics other than atosiban (e.g., transfers from other care units) during their current episode of preterm labor may be eligible for the study. Historical failure of a tocolytic treatment in a previous episode of preterm labor is not a required inclusion criterion. Tocolytic failure is defined by progressive cervical changes or continuing uterine contractions

4.3. Exclusion Criteria

Deviations from 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.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Fever with a temperature greater than 100.4°F (38°C) for more than 1 hour or $\geq 101^\circ\text{F}$ (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, 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. Women with documented active hepatitis B or hepatitis C viral infection, unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
11. History of sensitivity to the IPs or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK/PPD medical monitor, contraindicates their participation.

4.4. Withdrawal From Study and Discontinuation of IP

The section describes and distinguishes the following:

- Withdrawal of the subject from the study after randomization but before administration of IP (Section 4.4.1.1) and after administration of IP (Section 4.4.1.2)
- Discontinuation of the IP (Section 4.4.2), 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.

4.4.1. Withdrawal From Study

4.4.1.1. 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 ECG cannot be dosed and should 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.

Dosing may be started before local liver function test results are available; however, if local laboratory results are available before the start of dosing and ALT is $>2 \times$ the upper limit of normal (ULN) or bilirubin is $>1.5 \times$ ULN ($>35\%$ direct bilirubin), the subject should not be dosed and should be withdrawn from the study. An isolated bilirubin $>1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin is $<35\%$. See Section 6.3.1 for liver stopping criteria for management of abnormal test results that become available after the start of dosing.

4.4.1.2. 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 GSK/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:

- Loss to follow-up
- Subject voluntarily withdrew consent
- Investigator decision to withdraw the subject from participation; investigators must consult the GSK/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 and before the Post-Infusion Assessment Phase will be asked to return and complete the assessments specified for the face-to-face post-infusion assessment visit before withdrawing from the study (see Section 3.1.3 and Table 5). If the subject withdraws after the face-to-face post-infusion assessment visit, the investigator will attempt to contact the subject by telephone to determine if she has delivered and to gather the information specified in Section 3.1.4.

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

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also 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 based on previous noncompliance.

In cases where the subject is deemed "Lost to Follow-up" (e.g., subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit), the investigator or designee should 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, then and only then will he/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.

4.4.2. 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
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. An abnormal corrected QT interval using 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 \geq 530 msec in a subject with a baseline QTcF value between 450 and 480 msec
6. Abnormal liver function test result detected during standard care of the subject based on the criteria detailed in Section 6.3.1.

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

Subjects discontinuing the IP who have not yet delivered will continue in the study through delivery and the maternal post-delivery assessment. 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.

4.5. Subject and Study Completion

A completed subject is defined as one who has completed all phases of the study (see Section 3.1 and Table 5). 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 4.4.2).

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.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

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. The solution for infusion should be stored refrigerated at 2°C to 8°C (36°F to 46°F), protected from light. Each single-use 5-mL vial contains 75 mg retosiban as solution for infusion (see Table 3). The contents of the label will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, retosiban IP 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. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

At the clinical study site, the volume required to make up the dose is withdrawn from 1 or more drug product vials and aseptically transferred into a 0.9% sodium chloride (NaCl) infusion bag to get the required concentration. The final mixture is a clear, colorless to slightly colored solution. The infusion solution is chemically stable for up to 48 hours under ambient conditions. Chemical stability up to 48 hours has also been established for the reconstituted and diluted solution in contact with representative IV administration sets under ambient conditions.

Atosiban (Tractocile, Ferring Pharmaceuticals) active comparator will be provided to the site. Atosiban is a marketed product that is a clear, colorless solution for infusion that contains atosiban at 6.75 mg/0.9 mL. Each single-use, 5-mL vial contains 37.5 mg of atosiban. The solution for infusion should be stored at 2°C to 8°C (36°F to 46°F), protected from light. Information on atosiban, including list of excipients, can be found in the product package inserts found in the summary of characteristics [Tractocile SmPC,

2013]. At the clinical study site, the volume required to make up the dose is withdrawn from 1 or several drug product vials and aseptically transferred into a 0.9% NaCl infusion bag to get the required concentration. The final mixture is a clear, colorless to slightly colored solution. The infusion solution is chemically stable for up to 24 hours under ambient conditions.

Because the IV dosing instructions for retosiban and atosiban differ, a double-dummy technique will be used to ensure blinding. For subjects randomized to retosiban, an unblinded pharmacist or other qualified individual will prepare the retosiban IV solution and a placebo infusion matched for the atosiban loading (bolus) dose and continuous infusion. Likewise, subjects randomized to atosiban will receive the atosiban loading (bolus) dose and continuous infusion and a placebo infusion matched for retosiban IV administration (see [Table 3](#); detailed instructions are provided in the Study Pharmacy Manual).

Atosiban solution for injection will be supplied by the unblinded pharmacist or other qualified individual as a prefilled syringe, whereas a prefilled syringe with 0.9% NaCl solution will be used for the matched placebo. Normal saline (0.9% NaCl) solution will be used for preparing the retosiban or atosiban admixtures for continuous infusion (see [Table 4](#)). Normal saline (0.9% NaCl) solution will also be used as the placebo solution matched to the infusion rates for retosiban or atosiban (see [Table 4](#); detailed instructions are provided in the Study Pharmacy Manual). The normal saline solutions will be provided by the investigative center.

Details of the dose preparation are described in the Pharmacy Reference Manual. The infusion bags and syringes containing the solution for administration will be clearly labeled by site staff with the protocol number, subject number, infusion rate, and dosing session number.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the IP will be limited to the investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

[Table 3](#) and [Table 4](#) summarize the retosiban and atosiban IP, respectively, and other study treatment.

Table 3 Retosiban Investigational Product and Other Study Treatment

Product Name	Retosiban 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
Preparation instructions	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 protocol number, subject number, infusion rate, and dosing session number. Once the vial has been opened, the dilution must be performed immediately. Diluted solution for IV administration should be used within 24 hours after preparation. If an infusion bag with a different volume is used, a proportional calculation should be made for the preparation. See the Study Pharmacy Manual for detailed instructions.	The placebo admixture will consist of a 0.9% NaCl infusion bag, labeled with the protocol number, subject number, infusion rate, and dosing session number. The volume of the 0.9% NaCl infusion bag should be matched to the 0.9% NaCl infusion bag volume used for the retosiban admixture. See Study Pharmacy Manual for detailed instructions.
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 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, investigators should administer another 6-mg loading dose by increasing the infusion rate to 240 mL/hour for 5 minutes, after which the	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 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, 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. Investigators will be required to indicate

Product Name	Retosiban Solution for Infusion	PTM IV Solution (0.9% NaCl)
	<p>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.</p> <p>For subjects receiving concomitant treatment with a potent 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.</p> <p>For subjects receiving concomitant treatment with a 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.</p> <p>A list of strong, moderate, and weak CYP3A4 inhibitors and inducers is provided in Appendix 3. See the Study Pharmacy Manual for detailed instructions.</p>	<p>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.</p> <p>For subjects receiving concomitant treatment with a potent 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.</p> <p>For subjects receiving concomitant treatment with a 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.</p> <p>A list of strong, moderate, and weak CYP3A4 inhibitors and inducers is provided in Appendix 3. See Study Pharmacy Manual for detailed instructions.</p>
Manufacturer / Source of procurement	GSK	Not applicable – to be sourced locally

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

Table 4 Atosiban Investigational Product and Other Study Treatment

Product Name	Atosiban Solution for Injection and Atosiban Solution for Infusion	PTM IV Solution (0.9% NaCl)
Drug product description	Clear, colorless solution for injection in a 0.9-mL vial containing 6.75 mg of atosiban Clear, colorless concentrate for solution for infusion in a 5-mL vial containing 37.5 mg atosiban	A placebo-matched 0.9-mL vial is not provided. A placebo-matched 5-mL vial is not provided.
Unit dose strengths / Dosage levels	Atosiban 6.75 mg/0.9 mL (solution for injection) Atosiban 7.5 mg/mL (concentrate solution for infusion) The total dose given over 48 hours should not exceed 330 mg.	0.9% NaCl for injection matched for the atosiban loading dose and continuous infusion rates
Route of administration	IV	IV
Preparation instructions	Withdraw 0.9 mL of a 0.9-mL labeled vial of atosiban 6.75 mg/0.9 mL solution for injection into a syringe. Label the syringe with the protocol number, subject number, infusion rate, and dosing session number. Withdraw 25-mL solution from a 250-mL 0.9% NaCl infusion bag and discard the solution. Replace the solution with 25 mL of atosiban 7.5-mg/mL concentrate solution for infusion from five 5-mL vials to obtain a concentration of 0.75 mg/mL (187.5 mg atosiban in 250 mL 0.9% NaCl). The reconstituted product is a clear, colorless solution without particles. Label the IV bag with protocol number, subject number, infusion rate, and dosing session number. Prepare new 250-mL bags in the same manner as described to allow the infusion to be continued. If an infusion bag with a different volume is used, a proportional calculation should be made for the preparation. Once the vial has been opened, the dilution must be performed immediately. Diluted solution for IV administration should be used within 24 hours after preparation. See the Study Pharmacy Manual for detailed instructions.	Withdraw 0.9 mL of 0.9% NaCl solution for injection into a syringe. Label the syringe with the protocol number, subject number, infusion rate, and dosing session number. The placebo admixture for continuous infusion will consist of a 0.9% NaCl infusion bag, labeled with the protocol number, subject number, infusion rate, and dosing session number. The volume of the 0.9% NaCl infusion bag should be matched to the 0.9% NaCl infusion bag volume used for the atosiban admixture. See Study Pharmacy Manual for detailed instructions

Product Name	Atosiban Solution for Injection and Atosiban Solution for Infusion	PTM IV Solution (0.9% NaCl)
Dosing instructions	<p>Atosiban is administered in 3 successive stages.</p> <p>Administer an initial bolus dose of 6.75 mg slowly over 1 minute using the 6.75-mg/0.9 mL solution for injection syringe.</p> <p>After the bolus dose, administer atosiban at a continuous infusion rate of 24 mL/hour (18 mg/hour) for 3 hours.</p> <p>After 3 hours, the infusion rate is reduced to 8 mL/hour (6 mg/hour) for the remainder of the 48-hour treatment period.</p> <p>See the Study Pharmacy Manual for detailed instructions.</p>	<p>The matched placebo is administered in 3 successive stages.</p> <p>Using a prefilled syringe, administer 0.9 mL of 0.9% NaCl slowly over 1 minute.</p> <p>After the bolus dose, administer 0.9% NaCl at a continuous infusion rate of 24 mL/hour for 3 hours.</p> <p>After 3 hours, the infusion rate is reduced to 8 mL/hour for the remainder of the 48-hour treatment period.</p> <p>See Study Pharmacy Manual for detailed instructions.</p>
Manufacturer / Source of procurement	To be sourced locally	Not applicable – to be sourced locally

IV = intravenous; NaCl = sodium chloride; PTM = placebo to match.

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

5.1.1.1. Retosiban

Retosiban undergoes oxidative metabolism, primarily mediated by CYP3A4 (see Section 3.2.1.1). 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 AUC, in the presence of ketoconazole, a strong CYP3A4 inhibitor.

To achieve exposures comparable 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 5.8.1.5). Using a 500-mL retosiban admixture with a 0.3-mg/mL concentration, the retosiban 3-mg loading dose will be administered at an infusion rate of 120 mL/hour for 5 minutes. After 5 minutes, the infusion rate will be reduced to 6.7 mL/hour to deliver retosiban at a rate of 2 mg/hour. If a dose increase is needed due to lack of response, an additional loading dose of 1 mg over 5 minutes followed by an increase to 3 mg/hour for the remainder of the 48-hour treatment period is an acceptable dosing regimen to use in the presence of a strong CYP3A4 inhibitor.

For subjects chronically taking a drug known to be a 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. If a dose increase is needed due to lack of response, an additional 3.5-mg loading dose over 5 minutes should be administered followed by an increase to 12 mg/hour for the remainder of the 48-hour treatment period.

A list of strong, moderate, and weak CYP3A4 inhibitors and inducers is provided in [Appendix 3](#).

5.1.1.2. Atosiban

Atosiban is unlikely to involve CYP-mediated drug-drug interactions, as *in vitro* investigations have shown that atosiban is not a substrate for the CYP system and does not inhibit the drug metabolizing CYP enzymes [[Tractocile SmPC](#), 2013].

5.2. Managing Dose Interruptions

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

For atosiban dose interruptions, resume the infusion at the same rate that was used before the dose interruption.

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

5.3. 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 atosiban using an interactive voice response system (IVRS)/interactive web response system (IWRS) in accordance with the randomization schedule.

Retosiban and atosiban regimens are described in [Table 3](#) and [Table 4](#). The IP will be administered by study personnel during each dosing session.

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. Infusion and dose administration information can be found in the SPM and Study Pharmacy Manual.

5.4. Blinding

The pharmacist or other qualified individual will be unblinded, and an unblinded clinical research associate will carry out drug 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 as part of a formal interim analysis and in accordance with the IDMC charter. Unblinded data will be provided by an independent statistical data analysis committee.

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.

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 clinical investigators in accordance with local regulations and/or GSK policy.

5.5. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of IP dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

5.6. Treatment Compliance

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.

5.7. 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).

5.8. 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.

5.8.1. Permitted Medications and Nondrug Therapies**5.8.1.1. Antenatal Corticosteroids**

Antenatal corticosteroid treatment should be administered in accordance with national, society, or institutional guidelines.

5.8.1.2. Magnesium Sulfate

Magnesium sulfate for fetal neuroprotection is permitted at the investigator's discretion according to national, society, or local guidelines and/or approved prescribing information.

5.8.1.3. Progesterone

Progesterone may be continued for subjects already on established progesterone therapy but should not be initiated in subjects after they have been enrolled in the study.

5.8.1.4. Antibiotics

Antibiotic treatment for GBS is allowed per institutional guidelines.

5.8.1.5. Strong CYP3A4 Inhibitors

Drugs that are strong CYP3A4 inhibitors and cannot be temporarily discontinued are permitted. Administration of strong CYP3A4 inhibitors concomitantly with IP requires an adjustment to the retosiban dosing regimen (see Section 5.1.1). A list of strong, moderate, and weak CYP3A4 inhibitors is provided in [Appendix 3](#).

5.8.1.6. Strong CYP3A4 Inducers

Drugs that are strong CYP3A4 inducers and cannot be temporarily discontinued are permitted. Administration of strong CYP3A4 inducers concomitantly with IP requires an adjustment to the retosiban dosing regimen (see Section 5.1.1). A list of strong, moderate, and weak CYP3A4 inducers is provided in [Appendix 3](#).

5.8.1.7. 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. No dose adjustment is required; concomitant use of retosiban with inhibitors of BCRP or P-gp will be assessed through AE monitoring. A list of BCRP and P-gp inhibitors is provided in the SPM.

5.8.2. 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 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.

5.9. 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.

Poststudy IP is not provided as part of this protocol.

5.10. Treatment of Study Treatment Overdose

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

Few cases of atosiban overdosing have been reported, and these occurred without any specific signs or symptoms. There is no known specific treatment in case of an atosiban overdose [[Tractocile](#) SmPC, 2013].

6. STUDY ASSESSMENTS AND PROCEDURES

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 pregnancy history, and estimated GA). However, the subject will be required to provide 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. A schedule of Time and Events is provided in [Table 5](#).

Table 5 Time and Events Table

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery ³	Delivery to 28 days post EDD	
Clinical and Other Assessments										
Written informed consent and medical releases for treatment ⁴	X									
Discuss and request consent for participation in the infant follow-up study ⁵		<div>X⁵←──</div>								

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery ³	Delivery to 28 days post EDD	
Determine AFI via ultrasound ⁹	X			X						
Uterine contractions ¹⁰	X									
Schedule face-to-face post-infusion assessment visit			X							
Investigational Products¹¹										
Investigational product (retosiban or atosiban)		X	X	X						
Efficacy Assessments										
Date and time of delivery							X ¹²			
Mode of delivery							X ¹²			
Indication for delivery							X ¹²			
Neonatal composite outcomes									X	
Neonatal hospital stay									X	

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery ³	Delivery to 28 days post EDD	
Maternal Safety Assessments										
Concomitant medications			X					X		X
ECG 12-lead ¹³	X									
Vital sign measurements (BP, pulse rate, respiratory rate, and temperature) ¹⁴	X	X	X	X	X					
AEs, SAEs, and DREs: maternal			X					X		X
Breastfeeding status								X		
Edinburgh Postnatal Depression Scale ¹⁵ (maternal)								X		
Local laboratory assessments (LFTs only) ¹⁶	X			X						
Central laboratory assessments (including hematology, chemistry, and LFTs) ¹⁷	X		X	X	X ¹⁷					
Physical examination (brief)					X					
Status of postpartum bleeding								X		

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery ³	Delivery to 28 days post EDD	
Fetal Safety Assessments										
Electronic fetal monitoring	X ¹⁸	X ¹⁹	X ¹⁹	X ¹⁹	X ²⁰		X ²¹			
AEs/SAEs: fetal			X				X			
Neonatal Safety Assessments										
AEs, SAEs, and DREs: neonatal							X		X	
Neonatal Apgar Scores (1 and 5 minutes)							X ¹²			
Neonatal growth parameters							X ¹²			
Neonatal blood gases							X ¹²			
Health Outcome Assessments										
Maternal and neonatal health care resource use ²²							X		X	
EQ-5D-5L (maternal)		X						X ³		
Pharmacokinetic Assessments										
Maternal PK blood sample ²³		X ²³	X ²³							
Cord blood sample ²⁴							X			
Breast milk/colostrum sample ²⁵							X			
Histopathology										
Placental tissue sample ²⁶							X			

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery ³	Delivery to 28 days post EDD	
Biomarker Assessments										
Genetic blood sample for maternal DNA ²⁷	X									
Blood sample for maternal inflammation biomarker	X									
Biomarker and genetic cord blood sample ²⁸							X			
Other Assessments										
Fetal fibronectin (optional) ²⁹	X			X						
Cervical length via transvaginal ultrasound (optional) ³⁰	X			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; EPDS = Edinburgh Postnatal Depression Scale; EQ-5D-5L = EuroQoL 5-dimensional 5-level questionnaire; IP = investigational product; LFT = liver function test; PK = pharmacokinetic; SAE = serious adverse event; ULN = upper limit of normal.

- For undelivered subjects who are subsequently diagnosed with recurrent preterm labor 24 hours or more following completion of the Inpatient Randomized Treatment Phase, retreatment with blinded IP is permitted at the discretion of the investigator (see Section 3.1.3.1).
- Subjects who remain undelivered after 48 hours will return for a face-to-face post-infusion assessment visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase. (Note: study documents may reference this visit as the 1-week face-to-face post-infusion assessment visit). The subject will then be contacted every week via telephone to determine 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. If the subject delivers the baby prior to the face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and LFTs and the assessments for the Delivery Phase (see Section 3.1.4) will be performed.

3. 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) and the EQ-5D-5L (-2 weeks/ $+6$ weeks) (see Section 3.1.5 for list of assessments and visit windows).
4. 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.
5. The subject or other legal guardian for the infant will be asked to consent to participate in a separate long-term study to follow infants for safety and neurodevelopment outcomes. The subject or other legal guardian for the infant (both delivered and undelivered) will be asked to give consent for the infant follow-up study at any time during the study that is appropriate and convenient. Withdrawal from the study after beginning randomized treatment or discontinuing IP does not preclude involvement in the infant follow-up study.
6. 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.
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. Additional cervical examinations (Day 1, Day 2, and/or at the 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 4.2), 2 examinations must be documented (either 2 digital cervical examinations or 2 cervical length examinations).
8. An ultrasound for estimation of fetal weight and head circumference is needed at Screening or before retreatment 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 or the date of retreatment.
9. The abdominal ultrasound for determination of the AFI will be performed at Screening and before retreatment. The AFI should be measured using the 4-quadrant method.
10. 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.
11. Antenatal corticosteroid treatment should be administered in accordance with national, society, or institutional guidelines. Magnesium sulfate for fetal neuroprotection can be given at the discretion of the investigator.
12. Information regarding delivery will be obtained through a review of the hospital and medical records. Growth parameters include neonatal weight, length, and head circumference.
13. 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.
14. Vital signs (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, if criteria are met, also during retreatment, and at the post-infusion assessment visit. During the Inpatient Randomized Treatment Phase and during retreatment, vital signs will be assessed and recorded within the following windows relative to the start of the infusion: 15 to 30 minutes, 4 to 8 hours, and 20 to 24 hours, at the end of the infusion, at the time of any dose changes, and as warranted by a medical condition. It is suggested (but not required) that oxygen saturation also be assessed at Screening and recorded in source documents.
15. Maternal subjects will complete the EPDS, a self-reported questionnaire, at the maternal follow-up assessment 6 weeks (-2 weeks/ $+6$ weeks) after delivery.
16. 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 $\geq 2 \times \text{ULN}$ OR total bilirubin is not $>1.5 \times \text{ULN}$ ($>35\%$ direct bilirubin). An isolated bilirubin $>1.5 \times \text{ULN}$ 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 or for the start of dosing with IP; however, see Section 6.3.1 if ALT or bilirubin is abnormal.

17. 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 6.3.1). 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. 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.
18. Prior to dosing, if the fetal heart rate pattern is nonreassuring, the subject cannot be dosed.
19. 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 6.3.12.3).
20. If the subject has not delivered at the end of the Inpatient Randomized Treatment Phase, fetal heart rate (fetal Doppler heart rate or cardiotocography are both acceptable) 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 6.3.12.3).
21. 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 6.3.12.3).
22. 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.
23. PK samples will be taken at the following sampling windows (relative to the start of the infusion): 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. A maternal blood sample should be collected at the same time as the cord blood sample (see Section 6.5.1) if the sample time does not already coincide with one of the PK sampling windows.
24. In subjects who deliver at an investigative center within 12 hours following completion or discontinuation of the IP, the cord blood sample will also be divided for PK analysis as well as genetic (if additional consent is provided; see Appendix 1) and biomarker analyses.
25. 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.
26. A placental tissue sample will be collected at delivery in subjects who deliver at an investigative center.
27. A maternal blood sample for genetic research will only be collected from subjects who provide separate informed consent (see Appendix 1).
28. A cord blood sample will be collected in subjects who deliver at an investigative center, if additional consent is provided.
29. Testing for fetal fibronectin will be performed only at those institutions collecting the information as routine practice. Fetal fibronectin will not be used to determine study eligibility.
30. Cervical length measured by transvaginal ultrasound will be captured only at those institutions collecting the information as routine practice. Cervical length will not be used to determine study eligibility.

6.1. 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 $\geq 2 \times \text{ULN}$ OR bilirubin is not $> 1.5 \times \text{ULN}$ ($> 35\%$ direct bilirubin), if available (see Section 6.3.1). An isolated bilirubin $> 1.5 \times \text{ULN}$ is acceptable if bilirubin is fractionated and direct bilirubin is $< 35\%$. Dosing may be started prior to the availability of these results.
- 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 4.4.1).

6.2. Efficacy

Collection of efficacy endpoint data requires a thorough review of the hospital medical records. Review of the maternal hospital record is the responsibility of the investigator obstetrician and review of the newborn hospital record is the responsibility of the subinvestigator neonatologist.

6.2.1. 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.

6.2.2. 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 6.2.4)
- Hospital length of stay
- Neonatal admission to a specialized care unit and length of stay
- Newborn hospital readmission and length of stay
- Ambulatory surgery

6.2.3. Primary Efficacy Endpoint

The primary efficacy endpoint is time to delivery from the start of IP administration until delivery, based on a records review.

6.2.4. Key Secondary Efficacy Endpoints

- Proportion of births prior to 37^{0/7} weeks' gestation – ascertain the GA at delivery based on a records review
- Proportion of births at term (37^{0/7} to 41^{6/7} weeks' gestation) – ascertain the GA at delivery based on a records review
- Length of neonatal hospital stay – confirm duration (in days) of neonatal hospital admission from the medical records
- Proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite determined up to 28 days after EDD (of 40^{0/7} weeks) – proportion of infants with any one of the following:
 - Fetal or neonatal death
 - 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 requirementOR
 - 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)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 cerebrospinal fluid culture performed as part of infection workup
- Retinopathy of prematurity
 - Confirmed by an ophthalmologist based on international committee Stage 4 or 5OR
 - Requiring surgical treatment with laser or other surgical intervention including cryotherapy or treatment with anti-VEGF (vascular endothelial growth factor)
- 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)

- Retosiban clearance and volume of distribution and the effect of covariates on these parameters

6.2.5. Other Secondary Efficacy Endpoints

- Proportion of neonates with any of the composite neonatal morbidity and mortality excluding RDS
- Proportion of neonates with each individual component of the composite neonatal morbidity and mortality endpoints listed in Section 6.2.4
- Neonatal admission to a specialized care unit and length of stay – confirm admission to neonatal intensive or specialized care unit from the medical records
- Newborn hospital readmission and length of stay – confirm any neonatal hospital readmission following the birth hospitalization, the reason for admission, and the length of stay from the medical records
- Ambulatory surgery – confirm any neonatal ambulatory surgery and the indication for surgery from the medical records
- Proportion of births prior to 28^{0/7} weeks' gestation
- Proportion of births prior to 32^{0/7} weeks' gestation
- Proportion of births ≤ 7 days
- Proportion of births ≤ 48 hours
- Proportion of births ≤ 24 hours

6.2.6. Exploratory Efficacy Endpoints

A complete list of exploratory endpoints will be provided in the reporting and analysis plan (RAP).

6.3. Safety

The timing for all safety assessments is outlined in the Time and Events Schedule Table 5.

Maternal:

- Incidence of reported AEs and SAEs
- Significant changes in vital signs and clinical laboratory tests
- Incidence of treatment-limiting toxicities including both clinical and laboratory etiology causing subject to discontinue study treatment

- Maternal AEs of special interest
 - Maternal death
 - Chorioamnionitis and its complications
 - Clinical chorioamnionitis, PPRM, endomyometritis, wound infection, pelvic abscess, bacteremia, septic shock, disseminated intravascular coagulation, and adult RDS
 - Placental abruption
 - Postpartum hemorrhage - postpartum hemorrhage and/or retained placenta (as assessed by AEs, time to expulsion of the placenta, assessment of uterotonic agents used, and change in hemoglobin from baseline value to 24 to 48 hours post-delivery adjusting for mode of delivery)
 - Pulmonary edema
- Incidence of women scoring 12 or higher on the EPDS

Fetal:

- Incidence of reported AEs, including 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](#), 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, and documentation of any complications
- Incidence of reported AEs and SAEs
- Neonatal AEs of special interest are of interest because of their relationship to maternal chorioamnionitis and will include the following:
 - Neonatal death
 - Asphyxia
 - Infections (early onset neonatal sepsis, septic shock, pneumonia, meningitis)
 - RDS
 - Hypotension

- IVH/periventricular leukomalacia with cysts or porencephaly
- Bronchopulmonary dysplasia
- Neonatal acidosis
- Hyperbilirubinemia
- Necrotizing enterocolitis (any modified Bell's staging criteria)
- Hypoxic ischemic encephalopathy

Maternal and neonatal disease-related events (DREs) to be reported are described in Section 6.3.7.

6.3.1. Liver Chemistry Stopping and Follow-Up 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 face-to-face post-infusion assessment visit for additional liver function testing in order 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>.

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:

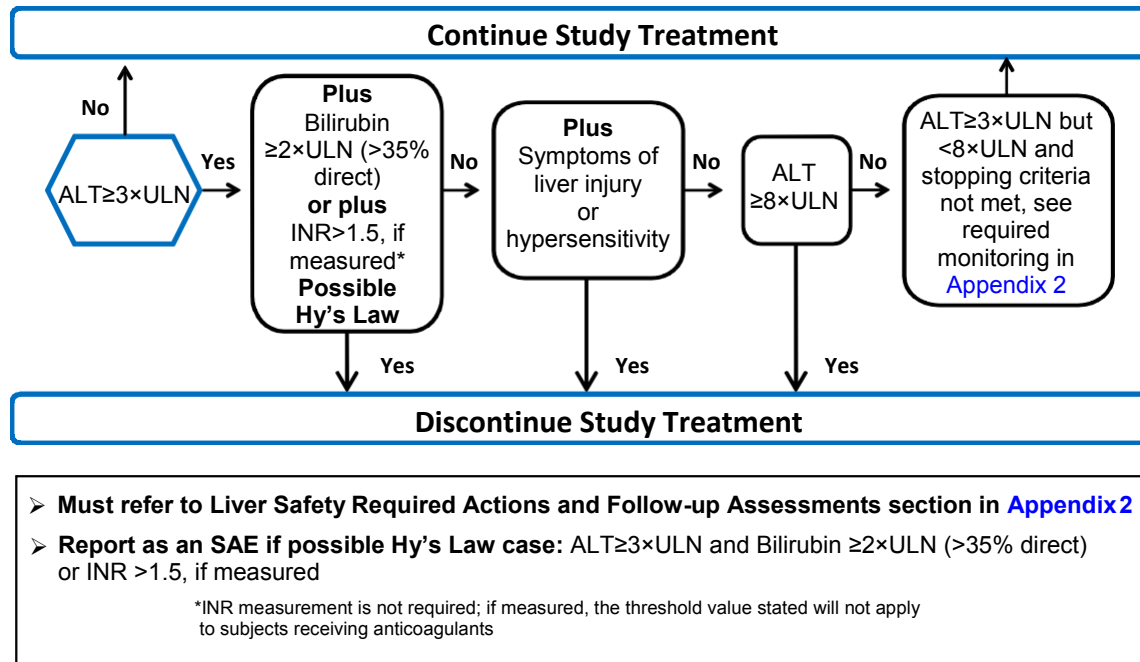
- $ALT \geq 2 \times ULN$ OR bilirubin $> 1.5 \times ULN$ ($> 35\%$ direct bilirubin). An isolated bilirubin $> 1.5 \times ULN$ is acceptable if bilirubin is fractionated and direct bilirubin is $< 35\%$.

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.

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

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



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](#).

6.3.1.1. 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.

6.3.2. Adverse Events

The investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. Separate reporting will be done for maternal, fetal, and neonatal AEs.

6.3.2.1. Definition of an AE

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. For marketed medicinal products, this

also includes failure to produce expected benefits (i.e., lack of efficacy), abuse, or misuse.

Events meeting the definition of an AE include:

- 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/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 that **do not** meet the definition of an AE include:

- 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

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.

6.3.2.2. Definition of an SAE

An SAE is any untoward medical occurrence that, at any dose:

- a. Results in death (maternal, fetal, or neonatal in this study)
- 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
- d. 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.

e. Results in disability/incapacity, or

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.

f. Is a congenital anomaly/birth defect

g. 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.

h. All events of possible drug-induced liver injury with hyperbilirubinemia defined as $ALT \geq 3 \times ULN$ and bilirubin $\geq 2 \times ULN$ ($>35\%$ direct) (or $ALT \geq 3 \times ULN$ and international normalized ratio (INR) >1.5 , if INR measured) termed “Hy’s Law” events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

NOTE: The central laboratory report will include results for ALT, AST, ALP, total bilirubin, and direct bilirubin.

6.3.2.3. 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 6.3. Guidelines for reporting these events are provided in [Appendix 4](#).

6.3.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements),

including those that worsen from baseline values, and felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs. However, any clinically significant 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, are **not** to be reported as AEs or SAEs.

6.3.4. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools 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
- Revascularisation

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.

6.3.5. Death Events

In addition, all deaths (maternal, fetal, and neonatal) will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

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.

6.3.6. 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 health 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.

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

The DREs listed in Section 6.3.7.1 and Section 6.3.7.2 will be monitored by an internal GSK safety review team (reviewing blinded data).

6.3.7.1. 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 6.3.7.2 applies
- Hospitalization for delivery, unless prolonged or 1 of the conditions listed at the end of Section 6.3.7.2 applies

6.3.7.2. 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 6.3.7.1 and Section 6.3.7.2) 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 an SAE). These events will be recorded on the DRE page in the eCRFs. 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 using the standard process, as summarized in Section 6.3.11:***

- 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 in an infant born ≥ 37 completed weeks.

If any of the above conditions are met, then record the event on the SAE page rather than the DRE page and report promptly (i.e., expedited reporting, see Section 6.3.11) to GSK/PPD.

6.3.8. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

Adverse events and SAEs will be collected from the start of study treatment and until the follow-up contact (see Section 6.3.10) 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 Section 6.3.11.

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.

6.3.9. Method of Detecting AEs and SAEs

Care must 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 the following:

“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?”

6.3.10. 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 6.3) 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 4.4.1.2). 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 the SPM.

6.3.11. Prompt Reporting of SAEs and Other Events to GSK/PPD

Serious AEs, nonserious AEs related to study treatment, and liver function abnormalities meeting predefined criteria will be reported promptly by the investigator to GSK/PPD as described in Table 6 once the investigator determines that the event meets the protocol definition for that event. Additional details describing DREs not qualifying as SAEs are described in Section 6.3.7.

Table 6 Reporting of Serious Adverse Events and Other Events to GSK/PPD

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular or death event	Initial and follow-up reports to be completed within 1 week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow-up reports to be completed within 1 week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Nonserious adverse events related to study treatment	5 calendar days	"Adverse Reaction" data collection tool	2 weeks	Updated "Adverse Reaction" data collection tool
DRE	2 weeks ¹	DRE eCRF	2 weeks ¹	Updated DRE eCRF
<i>Liver chemistry abnormalities</i>				
ALT \geq 3 x ULN and bilirubin \geq 2 x ULN (>35% direct) (or ALT \geq 3 x ULN and INR>1.5, if INR measured) ²	24 hours ³	"SAE" data collection tool. "Liver Event eCRF" and "Liver Imaging" and/or "Liver Biopsy" eCRFs, if applicable ⁴	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents ⁴
ALT \geq 8 x ULN; ALT \geq 3 x ULN with hepatitis or rash or \geq 3 x ULN and <5 x ULN that persists \geq 4 weeks	24 hours ³	"Liver Event" Documents (defined above) ⁴	24 hours	Updated "Liver Event" Documents ⁴

ALT = alanine aminotransferase, CV = cardiovascular; DRE = disease-related event, eCRF = electronic case report form; GSK = GlaxoSmithKline; INR = International normalized ratio, SAE = serious adverse event, ULN = upper limit of normal.

1. The study review team should determine the appropriate time frame, if one is needed, for completion of DRE eCRF pages
2. The INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.
3. GSK/PPD must be contacted at onset of liver chemistry elevations to discuss subject safety.
4. Liver Event Documents (i.e., "Liver Event eCRF" and "Liver Imaging eCRF" and/or "Liver Biopsy eCRF," as applicable) should be completed as soon as possible

The contact information for reporting SAEs is as follows:

Issue	All Countries/Regions Contact
Serious Adverse Event Reporting	24-Hour SAE Hotline: PPD SAE Fax: PPD

The method of recording, evaluating, and following up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK/PPD are provided in the SPM. Procedures for poststudy AEs/SAEs are provided in the SPM.

6.3.11.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK/PPD is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK/PPD 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, Institutional Review Board (IRB)/Independent Ethics Committee (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 an 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.

6.3.12. Other Safety Outcomes

6.3.12.1. Physical Examination

An admission physical examination will include at 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 face-to-face post-infusion assessment visit, following conclusion of the treatment phase.

6.3.12.2. Vital Sign Measurements

Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) will be measured at the following time points during the study: Screening, Inpatient Randomized Treatment Phase, retreatment (if criteria are met, see Section 3.1.3.1), and at the

face-to-face post-infusion assessment visit. During the Inpatient Randomized Treatment Phase and during retreatment, vital signs 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. It is suggested (but not required) that oxygen saturation also be assessed at Screening and recorded in source documents.

6.3.12.3. 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 bolus 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 6.3.12.2). The electronic fetal heart rate tracing (paper or electronic) must be archived and retained in site records. Fetal heart rate (fetal Doppler heart rate or cardiotocography are both acceptable) will be recorded at the 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, 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

6.3.12.4. 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 4.3). 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 ultrasound-derived estimated fetal weight and head circumference within 3 weeks of Screening, with the results and date of assessment recorded in the eCRF).

If the investigator determines a subject suitable for retreatment (see Section 3.1.3.1 for retreatment criteria), an abdominal ultrasound to assess fetal growth should be performed unless records are available documenting ultrasound-derived estimated fetal weight and

head circumference within 3 weeks of retreatment, with the results and date of assessment recorded in the eCRF.

6.3.12.5. Laboratory Assessments

The following laboratory tests will be performed locally:

- Liver function tests, including ALT and bilirubin, performed at Screening (see Section 6.3.1)

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 on the subject's eCRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

With the exception of the above, all protocol-required laboratory assessments, as defined in Table 5, must be performed by the central laboratory. For subjects that do 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.

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 biological samples collected over the course of the study that are directly related to the conduct and analysis of the study, including hematology and chemistry tests, and liver function tests are summarized further in Appendix 5.

6.3.12.6. 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. Performance of a follow-up ECG after an abnormal finding will be at the discretion of the investigator.

6.3.12.7. Breastfeeding Status

A questionnaire will be administered at the maternal post-delivery assessment to assess the status of breastfeeding, as appropriate.

Details regarding the questionnaire content and administration are provided the SPM.

6.3.12.8. Maternal Depression

The effect of preterm labor, the prevention of preterm labor, and the impact 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 study center personnel will be notified immediately in order to follow-up with the subject to ensure safety. Certain items in the scale also assess anxiety and will be used to assess level of anxiety. The EPDS will be administered to mothers 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.

6.4. Health Outcomes

- 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, 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, etc.), and surgical procedures.
- Assess maternal health status (EQ-5D-5L) at time of IP administration and 6 weeks (-2 weeks/+6 weeks) after delivery

6.4.1. Health Outcomes – Maternal

6.4.1.1. 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 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, Cesarean section).

6.4.1.2. Maternal Subject-Reported Health Assessments

The effect of preterm labor, the prevention of preterm labor, and the impact of preterm birth on maternal health status will be assessed using the EQ-5D-5L self-administered questionnaire:

- The EQ-5D-5L consists of 2 pages (the EQ-5D-5L descriptive system and the EQ visual analogue scale [EQ VAS]) plus a cover page. The descriptive system comprises mobility, self-care, usual activities, pain/discomfort, anxiety/depression, with each dimension having 5 response levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

The EQ VAS records the respondent's self-rated health on a 20-cm vertical, VAS with endpoints labeled "the best health you can imagine" and "the worst health you can imagine."

This information can be used as a quantitative measure of health as judged by the individual respondents. The EQ-5D-5L will be administered to mothers early in the drug delivery phase (while the mother is still in active preterm labor) and at the maternal follow-up assessment 6 weeks (-2 weeks/+6 weeks) after 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.

6.4.2. Health Outcomes – Neonatal

6.4.2.1. Neonatal Hospital Admission

For the delivery visit hospitalization, the length of the hospital stay (days) and associated hospital unit (NICU, nursery level, or level of care 1 to 4) will be 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.

6.4.2.2. Neonatal Health Care Resource Use

Details of neonatal health care resource use associated with neonatal comorbidities of interest will be 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

6.5. 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/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.

The samples collected for PK analyses are summarized further in [Appendix 5](#).

6.5.1. 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.

Additionally, a maternal blood sample should be collected at the same time as the cord blood sample (see Section [6.5.2](#)) 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.

6.5.2. Umbilical Cord Blood

For those subjects who deliver at the investigative center, a single cord blood sample will be collected and divided for biomarker assays (Section [6.8](#)) and potential genetic research (Section [6.9](#)). If subjects deliver at the investigative center within 12 hours following completion or discontinuation of IP, the cord blood sample will also be used for a PK assessment of fetal drug exposure. 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 sampling for the study.

Samples from retosiban-treated subjects with concomitant use of inhibitors of BCRP or P-gp will be analyzed for drug-drug interactions. The date and time of the sample should be noted in the eCRF.

6.5.3. 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 from receiving 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.

6.6. 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 will not be used to determine eligibility but 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.

6.7. Fetal Fibronectin

Institutions that routinely perform 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.

6.8. 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 maternal blood sample for biomarker research will be collected at Screening and a cord blood sample for biomarker research will be collected during the Delivery Phase. The samples will be stored and may be analyzed for future exploratory research.

The blood samples collected for biomarker analyses are summarized further in [Appendix 5](#).

6.9. Genetic Research

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. At Screening (Day 0), a 6-mL blood sample for maternal DNA will be collected in subjects who provide informed consent for genetic research. In addition, for

those subjects who deliver at the investigative center, a cord blood sample will also be collected for potential genetic assays.

Additional information regarding genetic research is included in [Appendix 1](#) and [Appendix 5](#).

7. 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. Adverse events and concomitant medications terms will be coded using the MedDRA and an internal validated medication dictionary, GSKDrug.

Electronic CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

The primary endpoint is prolongation of pregnancy as measured by time to delivery (days). The following are the null (H_0) and alternative (H_1) hypotheses for the primary endpoint in this study:

- H_0 : The prolongation of pregnancy as measured by time to delivery is equal between the women randomized to retosiban versus atosiban
- H_1 : The prolongation of pregnancy as measured by time to delivery is unequal between the women randomized to retosiban versus atosiban

The hypotheses will be tested at 5% level with a 2-sided test. 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 sequential testing method will be used to adjust for multiplicity of key secondary endpoints such that the type I error rate will be maintained at 5%. Refer to Section [8.3.5.1.2](#) for details of key secondary analysis.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

A total of 330 women (165 women per treatment group) will be recruited into the study and randomly assigned to treatment to ensure that 300 women/newborns (150 women/newborns per treatment group, assuming 10% missing data) have recorded

birth data, which provides 86% statistical power to detect an average difference of 9.5 days between retosiban and atosiban in time to delivery in the proposed adaptive design with futility analysis.

The above sample size calculations are based on a 2-sided testing procedure with a type I error rate of 5% and an approximate 10% dropout rate. Calculations are based on simulations and assumes 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 atosiban treatment group will deliver within the 3 weeks of GA at randomization. The details of the model assumption and simulation are included in a supplemental simulation report.

Statistical Operating Characteristics

Simulations were carried out to determine the statistical properties for inference about the primary hypothesis of the adaptive design with regard to the control of the overall type I error and the statistical power under a wide range of efficacy for retosiban, from no effect (i.e., null hypotheses) to an increase of 9.5 days in time to delivery (i.e., alternative hypothesis) and to greater than expected efficacy. It was shown that the overall type I error rate (2.4%) was maintained at a level well below the 5% for the primary hypothesis. Furthermore, if the true effect of retosiban is small or zero, there is good probability (74%) that the study will be stopped early for lack of efficacy (i.e., futility). If the true effect of retosiban is as expected, the statistical power will be 86%, with a 7% probability that the study will be stopped for lack of efficacy. The details of model assumption and simulation are included in a supplemental simulation report.

Table 7 Operating Characteristics of the Adaptive Design Under the Null and Alternative Hypotheses

Case Hypothesis	Interim Analysis	Final	
	Futility	Failure	Success
Null (0 day)	74%	24%	2.4%
Alternative (9.5 days)	7%	7%	86%

8.2.2. Sample Size Sensitivity

It is expected that the time to delivery will be dependent on the percentage of women enrolled into each of the GA strata and the percentage of women that deliver within 3 weeks of randomization. Subsequently, the power of the study 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 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. If the proportion of women delivering within 3 weeks is 45%, 10% lower than expected, the power of the study will be approximately 75% to detect an average difference of 7.7 days between retosiban and atosiban in the time to delivery. If it is significantly lower, such as 20% lower, the power of the study

could be as low as 53% to detect an average difference of 5.8 days between retosiban and atosiban in the time to delivery. Details will be included in a supplemental simulation report.

8.2.3. Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations (Maternal)

8.3.1.1. 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.

8.3.1.2. 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 irrespective of their compliance to the planned course of treatment. Subjects who are randomly assigned but fail to receive any study treatment (as described in Section 4.4.1.1) 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.

8.3.1.3. 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 failure to meet inclusion criteria specified by the protocol.

8.3.2. Analysis Population (Neonatal)

8.3.2.1. 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.

8.3.2.2. 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 irrespective

of their compliance to the planned course of treatment. This is the primary analysis data set and will be used for evaluation of all neonatal efficacy endpoints.

8.3.2.3. Neonatal Per-Protocol Population

This Neonatal Per-Protocol Population is defined as all subjects in the Neonatal ITT Population excluding those who are major protocol violators.

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

The primary comparison of interest is retosiban versus atosiban for time to delivery based on the ITT population, at the 2-sided 5% level.

8.3.3.2. Other Comparisons of Interest

For each of the secondary endpoints, the comparison of interest is retosiban versus atosiban at the 2-sided 5% level. Other comparisons of exploratory endpoints between retosiban and atosiban will be discussed in the RAP.

8.3.3.3. Subgroup Analysis

Additionally, comparisons of retosiban versus atosiban for 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)

Other potential subgroup comparisons will be described in the RAP.

8.3.3.4. 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, other concomitant medications, etc. Details of analysis will be included in final RAP.

8.3.4. Interim Analysis

To ensure mother and infant safety, an IDMC will be used to periodically monitor the benefit:risk profile of subjects in the study. Safety and efficacy summaries will be provided to the IDMC by an independent statistical data analysis center. The IDMC will review periodic data to monitor potential benefit:risk profiles of the study intervention. With considerations for safety, recommendations may be made to modify the protocol or discontinue the study if any untoward events or pattern of events are detected.

There will be single planned interim analysis when approximately 130 subjects (65 subjects per treatment group) have completed delivery and have time-to-delivery results available. The primary objective of the interim analysis will be to determine if the

study will be terminated for lack of efficacy (futility) based on prespecified criteria. The decision will be based primarily on the analysis of the primary endpoint, time to delivery; however, all available safety and efficacy data will be reviewed.

Time to delivery will be analyzed as described in Section 8.3.5.1.1. An estimate of the difference in time to delivery between the retosiban and atosiban treatment group 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.

Full details of the statistical analysis and prespecified decision rules will be provided. The responsibilities of the IDMC and statistical data analysis center, as well as full details of the specific summaries and analyses of safety and efficacy data to be reviewed (including tables, listings, and summaries) will be provided in either the IDMC charter or the specific RAP for the IDMC.

8.3.5. Key Elements of Analysis Plan

8.3.5.1. Efficacy Analyses

8.3.5.1.1. Primary Analysis

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 atosiban in time to delivery versus the alternative hypothesis that there is a difference.

The primary analysis of time to delivery will utilize a finite mixture model [McLachlan, 2000] with 2 components, 1 for those women that delivery imminently and the other for the women delivering at term. The exact weight of each component will be determined by the observations from the component and model concomitant variables including treatment and GA at randomization. Within each component, the expected time to delivery will be modeled as a function of treatment as fixed effect and GA at randomization and established progesterone use (yes or no) as a covariate. The model parameters will be estimated using expectation-maximization algorithm. Point estimates, associated 95% CIs, and p-values for the overall average difference in time to delivery between retosiban and atosiban will be derived using the weighted average of model parameter estimates and variance from each subpopulation of mixture model. Details of mathematical model and analysis will be included in the RAP.

8.3.5.1.2. Secondary Analysis

Key Secondary Analysis

The key secondary analysis for this study includes 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), length of neonatal hospital stay, and composite neonatal morbidity and mortality. 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 sequential testing method 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 sequential testing examines the

hypothesis testing in a prespecified order, i.e., the testing of the second secondary endpoint will be performed only if the first secondary endpoint is significant at 5%, and testing of the third secondary endpoint will be performed only if the first and second endpoints are significant at 5%. The exact order of sequential testing will be detailed in the RAP.

For the endpoints of neonatal composite outcome, 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), a logistic regression model will be used for comparing retosiban with atosiban, with GA at randomization and established progesterone use (yes or no) as a covariate. 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 atosiban), 95% 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.

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 GA at randomization and established progesterone use (yes or no). 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 atosiban 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.

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.

8.3.5.2. Safety Analyses

No formal hypothesis statistical test will be performed for the safety data. All safety analyses will be done 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 atosiban treatment. As such, maternal, fetal, and neonatal safety data will be summarized by treatment group.

All summary statistics of continuous variables will include: n, 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, the following subgroups may be explored:

- GA of pregnancy at randomization
- Established progesterone use
- GA at delivery
- Maternal age
- Region/site

For each subgroup, maternal, fetal, and neonate safety data will be summarized by treatment and subgroup, as described above.

8.3.5.2.1. Extent of Exposure (Maternal)

The total volume administered during the infusion and the total volume administered overall will be 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 reason for discontinuation and who increased study treatment from 6 to 12 mg will be summarized.

8.3.5.2.2. 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, each phase of the study (pretreatment, treatment, and follow-up) will be tabulated 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 6.3.2.3) and DREs (see Section 6.3.7) will be similarly summarized.

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

8.3.5.3. Health Outcomes Analyses

Analysis of neonatal length of stay, one of the key secondary endpoints, is described in Section 8.3.5.1.2. 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 atosiban 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: n, 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
- Region/sites

8.3.5.4. 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.

8.3.5.5. Genetic Analyses

Any genetic analyses may be described in a separate genetic research analysis plan and may be reported separately from the main clinical study report. See [Appendix 1](#) for details about the genetic research analysis plan.

9. STUDY CONDUCT CONSIDERATIONS

9.1. 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.

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

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

The study will be conducted in accordance with all applicable regulatory requirements.

The study will 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, including, but not limited to:

- IRB/IEC review and favorable opinion/approval of study protocol and any subsequent amendments
- Subject informed consent

- Investigator reporting requirements

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

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., genetic research assessments described in [Appendix 1](#), unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, 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 include identification, agreement, and documentation of data items for which the eCRF will serve as the source document.

PPD will monitor the study to ensure 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) agrees to allow the monitor direct access to all relevant documents.

9.4. 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.

9.5. Study and Site Closure

Upon completion or termination of the study, the PPD monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK/PPD standard operating procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK/PPD will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. GSK/PPD will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or 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 easily accessible 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 the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must 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. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK/PPD will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK/PPD standard operating procedures, and/or institutional requirements.

The investigator must notify GSK/PPD of any changes in the archival arrangements, including, but not limited to, archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, Posting of Information on Publicly 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 results summary will be posted to the Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit. When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

A manuscript will be prepared for publication in the scientific literature if the results provide important scientific or medical knowledge.

9.8. 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.

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11. APPENDICES

11.1. Appendix 1: Genetic Research

Genetic Research Objectives and Analyses

- The objectives of the potential genetic research is to investigate a relationship between genetic factors and Response to medicine, including retosiban, atosiban, or any concomitant medications
- Preterm labor susceptibility, severity, progression, and related conditions

This research could include analyses of maternal/fetal gene interactions and the impact of genetic associations with preterm labor on drug response.

Genetic data may be generated while the clinical 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 utilize data collected in the clinical study and will be limited to understanding the objectives as highlighted here. 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 the reporting and analysis plan (RAP) prior to initiation of any analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical study report or in a separate genetics report, as appropriate.

Study Population

Any subject who is enrolled in the clinical 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. After the subject has provided informed consent for genetic research, the following procedures will be performed:

- Screening: blood samples will be collected for DNA extraction. Instructions for the collection and shipment of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed.
- Delivery: an additional sample of cord blood will be collected.

The genetic sample will be labeled (or “coded”) with the same study-specific number as used to label other laboratory 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 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 to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in genetic research may still participate in the clinical study. Informed consent specific for genetic research must be obtained before any blood sample for genetic research can be obtained.

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 research sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample will be retained for analysis
- Discontinue participation in genetic research and destroy the genetic DNA sample

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 clinical study or after completion of the clinical study, and it may be analyzed during the clinical study or stored for future analysis. If a subject withdraws consent for genetic research and genotype data have not been analyzed, the genetic DNA will not be analyzed or used for future research. If a subject withdraws consent for genetic research and genetic data have been analyzed, the genetic DNA will continue to be stored and used, as appropriate.

If a blood sample for genetic research has been collected and the subject is ultimately not dosed (see Section 4.4.1.1), then the investigator should instruct the participant 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.

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 clinical study, then the investigator should instruct the participant 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, or 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.

11.2. Appendix 2: Liver Chemistry Stopping and Follow-up Criteria

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-Absolute	ALT $\geq 8 \times$ ULN
ALT-Increase	ALT $\geq 5 \times$ ULN but $< 8 \times$ ULN persists for ≥ 2 weeks ALT $\geq 3 \times$ ULN but $< 5 \times$ ULN persists for ≥ 4 weeks
Bilirubin^{1,2}	ALT $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN ($> 35\%$ direct bilirubin)
INR²	ALT $\geq 3 \times$ ULN and INR > 1.5 , if INR measured
Cannot Monitor	ALT $\geq 5 \times$ ULN but $< 8 \times$ ULN and cannot be monitored weekly for ≥ 2 weeks ALT $\geq 3 \times$ ULN but $< 5 \times$ ULN and cannot be monitored weekly for ≥ 4 weeks
Symptomatic³	ALT $\geq 3 \times$ 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
<ul style="list-style-type: none"> 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 SAE² 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 	<ul style="list-style-type: none"> Viral hepatitis serology⁴ 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 antibody⁵ 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 $\geq 2 \times$ 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

<p>MONITORING:</p> <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> 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 <p><u>For all other criteria:</u></p> <ul style="list-style-type: none"> 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 	<p>including acetaminophen, herbal remedies, other over-the-counter medications.</p> <ul style="list-style-type: none"> Record alcohol use on the liver event alcohol intake case report form <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> 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.
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AE = adverse event; 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 $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ 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 $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN (>35% direct bilirubin) or ALT $\geq 3 \times$ 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 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
<p>ALT $\geq 5 \times$ ULN and $< 8 \times$ ULN and bilirubin $< 2 \times$ ULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT $\geq 3 \times$ ULN and $< 5 \times$ ULN and bilirubin $< 2 \times$ ULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.</p>	<ul style="list-style-type: none"> • 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 $\geq 5 \times$ ULN and $< 8 \times$ ULN to $\geq 3 \times$ ULN but $< 5 \times$ ULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT $< 3 \times$ ULN and bilirubin $< 2 \times$ 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.

11.3. Appendix 3: 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 5.1 and Section 5.1.1.1).

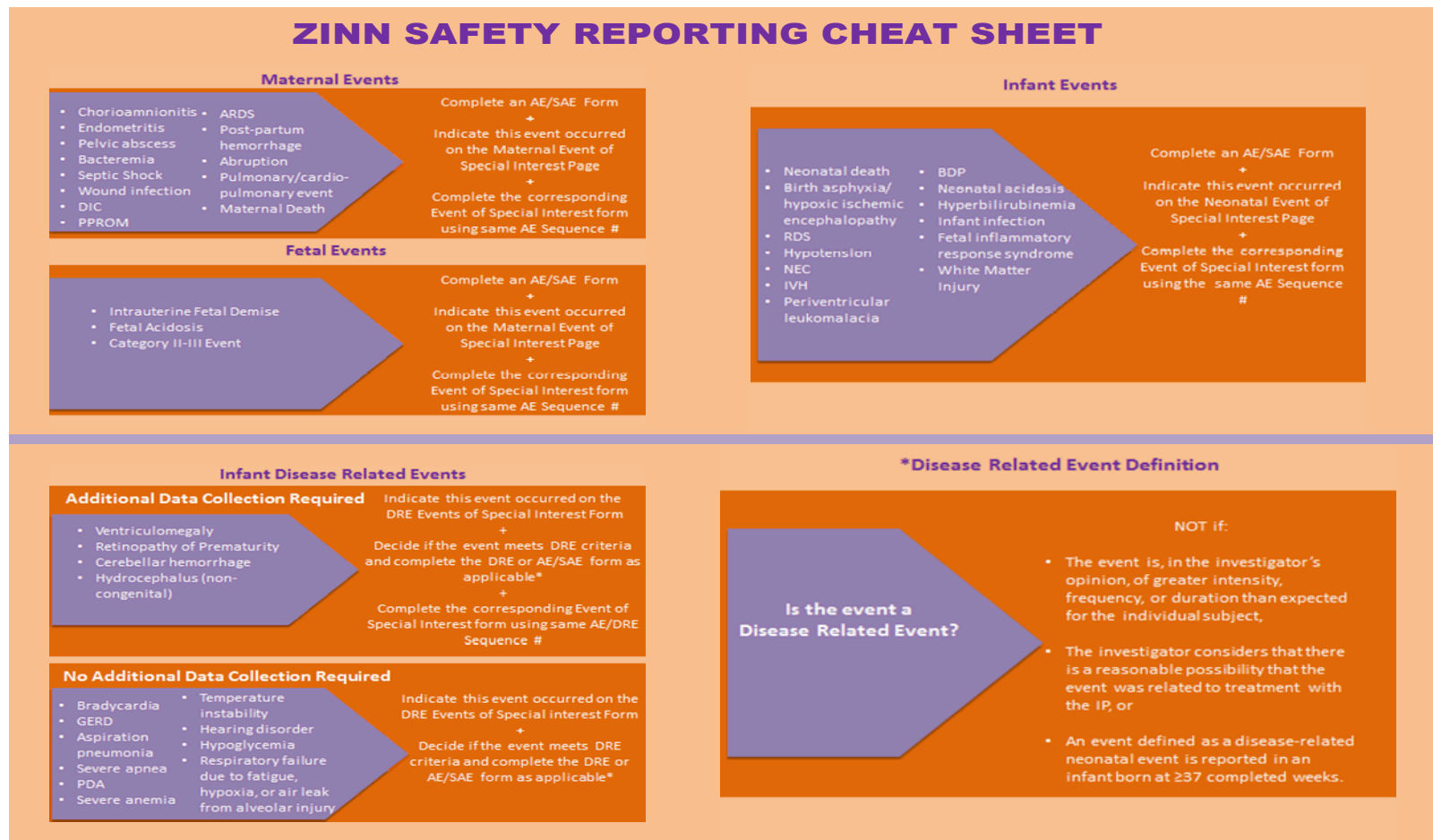
Following is a list of CYP3A4 inhibitors and inducers, each classified as strong, moderate, or weak on the basis of changes in the AUCi/AUC (area of the curve of substrate in the presence of an inhibitor/area under the curve of substrate in a control condition). This is not an exhaustive list; the summary 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.

Strong¹ (Requires Adjustment to Dosing Regimen)	Moderate²	Weak³
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

Strong¹ (Requires Adjustment to Dosing Regimen)	Moderate²	Weak³
		Propofol
		Quinidine
		Ranitidine
		Ranolazine
		Roxithromycin
		Tabimorelin
Inducers		
Strong¹ (Requires Adjustment to Dosing Regimen)	Moderate²	Weak³
Carbamazepine	Bosentan	Aprepitant
Efavirenz	Etravirine	Amprénavir
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 the investigational product with a strong inhibitor or strong inducer requires an adjustment to the retosiban 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.

11.4. Appendix 4: 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; PPRM = preterm premature rupture of membranes; RDS = respiratory distress syndrome; SAE = serious adverse event.

11.5. Appendix 5: Summary of Human Biological Samples

[Appendix 5](#) categorizes human biological samples as 1) those for which the results are directly related to the conduct and analysis of the study and 2) those collected and stored for future exploratory analyses. Human biological samples directly related to the study conduct and analysis include those for eligibility determination and safety, pharmacokinetics, and placental pathology. Human biological samples collected and stored for biomarker and genetic testing are categorized under future exploratory analyses. [Appendix 5](#) also provides information regarding labeling and subject anonymization. Shipping location information for each sample is provided in the Study Procedures Manual.

The investigator should refer to the laboratory manual for complete information on sample collection and preparation, packaging and labeling, and shipping.

Human Biological Samples Directly Related to the Conduct and Analysis of the Study:

- **Hematology and Chemistry:** Maternal blood samples for hematology and chemistry, including liver function studies, will be collected during Screening, Day 2 of dosing, at the optional retreatment visit (if applicable), and the face-to-face post-infusion assessment visit. Labels will be customized for each test and include the protocol number, subject identification number, visit description, and date and time of collection.
- **Liver Function:** A maternal blood sample for liver function studies will be collected during Screening and sent to the hospital laboratory for analysis. Normal results are required to initiate dosing or continue dosing if dosing has begun before results are available. In the event liver function test results from either the local or central laboratory reveal abnormalities consistent with the liver chemistry stopping criteria defined in Protocol Section 6.3.1 and [Appendix 2](#), additional samples will be analyzed for hepatitis A immunoglobulin M (IgM) antibody, hepatitis B surface antigen, hepatitis B core antibody (IgM), cytomegalovirus (CMV) IgM antibody, hepatitis C RNA, hepatitis E IgM antibody, Epstein-Barr viral (EBV) capsid antigen IgM antibody, creatine phosphokinase, lactate dehydrogenase, and complete blood count with differential.

If liver function test results reveal alanine aminotransferase (ALT) $\geq 3 \times$ the upper limit of normal (ULN) AND bilirubin $\geq 2 \times$ ULN (>35% direct bilirubin; an isolated bilirubin $> 1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin is $< 35\%$) samples will also be analyzed for the following:

- Antinuclear antibody, antismooth muscle antibody, type 1 antiliver kidney microsomal antibodies, and total immunoglobulin G (IgG)
- If chronic hepatitis B is identified at study entry by a positive hepatitis B surface antigen, blood samples will be assayed for hepatitis B DNA and hepatitis delta antibody.
- Serum acetaminophen in subjects with definite or likely acetaminophen use in the preceding week.

Labels will be customized for each test and include the protocol number, subject identification number, descriptor as initial liver event assessment or follow-up, and date and time of collection.

- **Pharmacokinetic Samples:**

1. Maternal blood samples for quantification of retosiban plasma concentrations will be collected 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 54 hours after initiation of the infusion.
2. An umbilical cord blood sample for quantification of retosiban plasma concentrations will be collected in subjects who deliver at the investigational center within 12 hours of investigation product (IP) completion or discontinuation. Additionally, a maternal blood sample should be collected at the same time as the cord blood sample (see Section 6.5.2) if the sample time does not already coincide with one of the PK sampling windows listed above.
3. A breast milk/colostrum sample for a semi-quantitative retosiban assay will be collected in subjects who deliver at the investigational center within 12 hours of IP completion or discontinuation and are expressing breast milk/colostrum.
4. Maternal blood sample for quantification of retosiban plasma concentration within 12 hours of exposure in subjects who meet liver chemistry stopping criteria defined in Protocol Section 6.3.1.

Labels will be customized for each test and include the protocol number, subject identification number, visit description, and date and time of collection.

- **Placental Pathology:** A placental tissue sample will be collected for pathologic examination **when** delivery occurs at an investigational center. Gross examination of the intact placenta, umbilical cord, and membranes will be performed by the hospital pathology department with gross findings reported in a standardized manner. The hospital pathology department will also prepare tissue samples for histologic examination of placenta, membranes, and umbilical cord. Labels will be customized and include the protocol number, subject identification number, visit description, and date and time of collection

Human Biological Samples for Optional Future Biomarker and Genetic Testing:

Biomarker and genetic testing will be performed in relation to the study treatment and preterm labor condition.

- **Biomarker Samples:**

1. Maternal blood samples for biomarker analysis will be collected for all subjects during Screening.
2. An umbilical cord blood sample for biomarker analysis will be collected in subjects who deliver at the investigational center.

Labels will be customized for each test and include the protocol number, subject identification number, visit description, and date and time of collection.

- **Genetic Samples:**

1. Maternal blood samples for genetic analysis will be collected during Screening for subjects who consent to participate. Refer to [Appendix 1](#) for a description of genetic testing objectives, assessments and procedures, subject participation, and confidentiality of data. Labels will be customized for each test and include the protocol number, subject identification number, visit description, and date and time of collection.
2. An umbilical cord blood sample for genetic analysis will be collected in subjects who deliver at the investigational center. Labels will be customized for each test and include the protocol number, subject identification number, visit description, and date and time of collection.

11.6. Appendix 6: Protocol Changes

Protocol Amendment Number 01 – Sites in France Only

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

- Inclusion criteria 1 and 2 were amended to specify that subjects must be at least 18 years of age to participate in Study 200721, and subjects who participate in Study 200721 must also agree to participate in Study 200722, a separate infant follow-up study.
- Text was revised throughout to reflect the change in the subject age criterion and the requirement to enroll in the infant follow-up study.
- Section 9.2 was updated to clarify that the study would be conducted using the current version of the Declaration of Helsinki.
- An appendix was added that categorizes laboratory samples into those supporting study conduct and those that may be analyzed at a later date.

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

Protocol Amendment Number 02 – Sites in United Kingdom Only

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

- The text from Section 5.3 (Blinding) was clarified. The intent of the language remains the same, but the clarification confirms there is no requirement for the investigator to discuss unblinding with the PPD medical monitor in order to rapidly unblind treatment for a study subject if needed.
- Section 9.2 was updated to clarify that the study would be conducted using the current version of the Declaration of Helsinki.

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

Protocol Amendment Number 03 – Sites in Sweden Only

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

- An appendix was added to list the medications considered strong, moderate, and weak CYP3A4 (cytochrome P450 3A4 enzyme) inhibitors and inducers.

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:

- Clarified the methods for documentation of 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 inclusion criteria for confirming sufficient dilation and effacement at Screening.
- Clarified that co-morbid medical or obstetric conditions that may exclude a subject from the study include known or suspected maternal Zika infection during gestation.
- Clarified the exclusion criterion for women with a history of substance abuse.
- Added an exclusion criterion for women for whom the combination of history and screening test results is suggestive of abuse or dependency.
- Clarified that withdrawal from the study will mean that no additional visits can occur or procedures performed.
- 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.
- Included a definition of inadequate treatment 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.
- Clarified the assessments performed at the 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, but this was not accurate as not all assessments originally indicated in the table will be performed during the weekly telephone calls. Additionally, the optional retreatment visit was added to the Time and Events Table and the assessments that will be performed when a subject withdraws from the study were clarified.
- Added definitions for a completed subject and study completion.

- Updated the atosiban preparation instructions for consistency with the pharmacy manual.
- Added 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.
- Clarified that there is no requirement for the investigator to discuss unblinding with the PPD medical monitor in order to rapidly unblind treatment for a study subject if needed.
- 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 presentation of the liver stopping criteria to more clearly summarize the criteria followed in the study and added that for local laboratory results an isolated bilirubin $>1.5 \times$ the upper limit of normal is acceptable if bilirubin is fractionated and direct bilirubin is $<35\%$.
- 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 study drug dosing. The protocol previously had not included that the 60-minute duration was relative to investigational product (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 measurements are assessed relative to dosing. Also, added an optional measurement of oxygen saturation at Screening only.
- Revised the timing of the pharmacokinetic (PK) sample taken at the onset of any maternal or fetal serious adverse event (SAE) from within 24 hours to within 12 hours after completion or discontinuation of IP.
- Clarified 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.

- Revised the visit window for the administration of the Edinburgh Postnatal Depression Scale (EPDS) and EuroQol 5-dimensional 5-level (EQ-5D-5L) from ± 2 weeks to -2 weeks/+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 and EQ-5D-5L up to 12 weeks after delivery.
- Added as a key secondary endpoint the PK analyses of retosiban clearance and volume of distribution and the effect of covariates on these parameters.
- Removed the listed exploratory endpoints and clarified that exploratory endpoints will be provided in the reporting and analysis plan.
- Removed the follow-up amniotic fluid index (AFI) by abdominal ultrasound as a fetal safety endpoint because requirement for an AFI by ultrasound 12 hours after completion of study treatment was removed.
- Removed from the list of disease-related maternal and neonatal events those events that were already listed as adverse events (AEs) of special interest.
- Clarified the time period and frequency of reporting AEs and SAEs.
- Updated the contact information for reporting SAEs.
- Added information for the follow-up of AEs and SAEs to clarify that all SAEs and nonserious AEs of special interest will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Additionally, added that any SAEs and AEs of special interest that are unresolved at 28 days post estimated date of delivery (EDD) should be followed to stabilization or resolution in those infants participating in the follow-up study.
- 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).
- Removed the requirement for an ultrasound for determination of the AFI within 12 hours of completion of study treatment.
- Revised the method used for adjusting multiplicity of the key secondary endpoints from a stepwise Holm's test to a sequential testing method.
- Added an appendix that provides guidelines for reporting maternal, fetal, and neonatal AEs of special interest, which is also provided in the SPM. This was added to provide sites ready access to these detailed guidelines.
- Incorporated the changes detailed in the country-specific amendment for sites in France (dated 29 Jan 2015).
- Incorporated the changes detailed in the country-specific amendment for sites in the United Kingdom (dated 29 Jan 2015).
- Incorporated the changes detailed in the country-specific amendment for sites in Sweden (dated 04 Feb 2015).

- 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]

Sponsor Information Page

Clinical Study Identifier: 200721 **(ZINN)**

Sponsor Medical Monitor Contact Information and Sponsor Serious Adverse Events (SAE) Contact Information:

Issue	Latin America Contact	Europe/Asia Contact
Safety Questions	PPD [REDACTED] MD Medical Director, Medical Affairs and Pharmacovigilance PPD Buenos Aires, Brazil	Europe: PPD [REDACTED] MD Associate Medical Director, Medical Affairs and Pharmacovigilance PPD Sofia, Bulgaria Asia: PPD [REDACTED] MD Associate Medical Director, Medical Affairs and Pharmacovigilance PPD Kuala Lumpur, Malaysia
SAE Reporting	24-Hour Safety Hotline: PPD [REDACTED] Safety Fax: PPD [REDACTED]	Safety Hotline: PPD [REDACTED] Safety Fax: PPD [REDACTED]
<u>SAE Reporting</u>	<u>24-Hour SAE Hotline:</u> PPD [REDACTED] <u>SAE Fax:</u> PPD [REDACTED]	

Investigator Protocol Agreement Page

For protocol 200721 **(ZINN)**

List of Abbreviations

IVRS interactive voice response system

IWRS interactive web response system

PCP phencyclidine**Definitions**

Estimated date of delivery	Defined as 40 ^{0/7} weeks' gestation for all subjects
Gestational age	Determined by (1) known fertilization date, either <i>in vitro</i> fertilization or intrauterine insemination; or (2) last menstrual period a best estimated due date confirmed or established by the earliest ultrasound performed prior to 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

Protocol Summary, Rationale

This study (**ZINN**) is designed to test this hypothesis through a direct comparison with atosiban, a mixed oxytocin-vasopressin antagonist indicated for short-term use to delay imminent preterm birth in women between 24^{0/7} and 33^{6/7} weeks' gestation in preterm labor.

Protocol Summary, Study Design

This **ZINN is a** Phase III ~~study will use a~~, randomized, double-blind, double-dummy, multicenter ~~design~~ **study**. Approximately 330 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, will be randomly assigned to retosiban or atosiban in a 1:1 ratio.

- Test Treatment: Retosiban

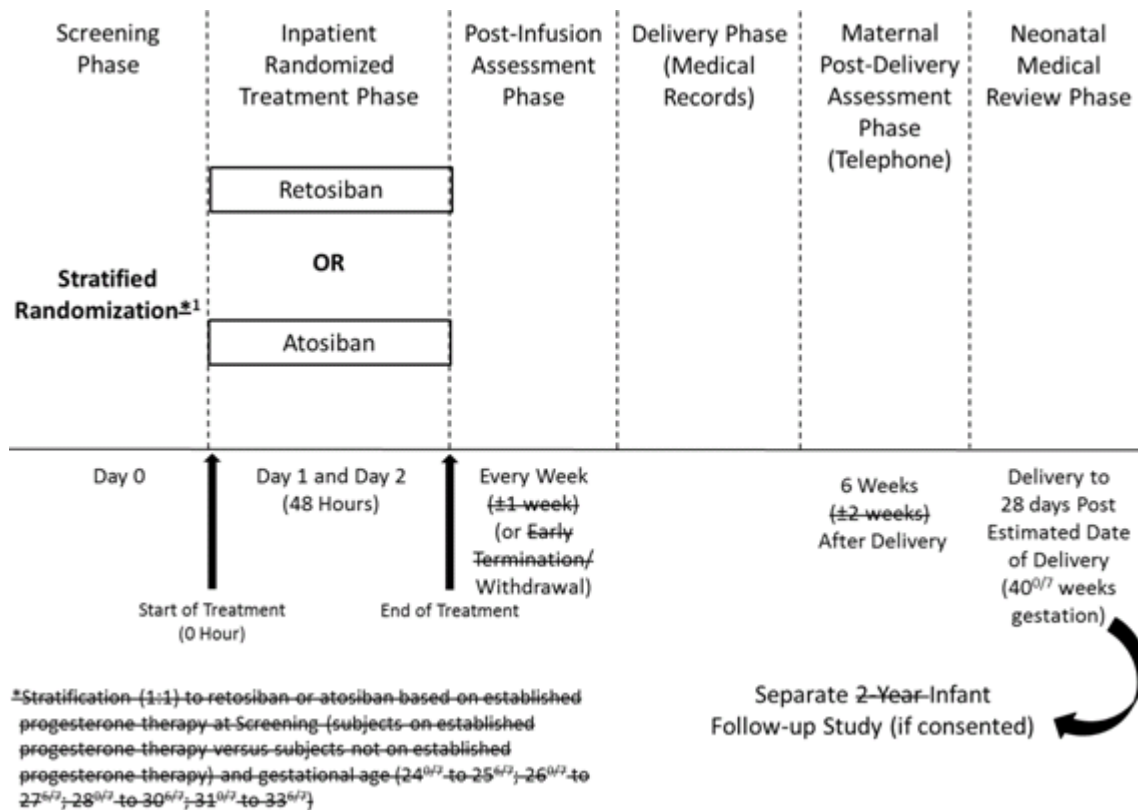
Retosiban treatment will be administered as a 6-mg IV loading dose over 5 minutes, followed by a 6-mg/hour continuous infusion over 48 hours. For subjects with an inadequate response **any time** after the first hour of treatment, investigators should increase the dose by another 6-mg IV loading dose and increase the infusion rate to 12 mg/hour for the remainder of the 48-hour treatment period (**for details see Table 3**).

- Active Control: Atosiban

Atosiban will be administered in 3 successive stages: an initial bolus dose (6.75 mg) over 1 minute, immediately followed by a continuous infusion at 18 mg/hour for 3 hours, followed by a 6-mg/hour infusion for the remainder of the 48-hour treatment period (**for details see Table 4**).

~~The study~~ **ZINN** will consist of 6 phases: Screening, Inpatient Randomized Treatment, Post-Infusion Assessment, Delivery, Maternal Post-Delivery Assessment, and Neonatal Medical Review (see schematic). The duration of any 1 subject's (maternal or neonatal)

participation in the study will be variable and dependent on GA at study entry and the date of delivery.



1. Stratification (1:1) to retosiban or atosiban 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. Subjects who have not delivered after 48 hours will return for a face-to-face post-infusion assessment 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 atosiban) is allowed.

Prior to randomization, each subject will be stratified by progesterone treatment and GA determined by (1) known fertilization date, either *in vitro* fertilization or intrauterine insemination; or (2) last menstrual period a best estimated due date confirmed or established by the earliest ultrasound prior to 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. 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}.

The Screening Phase will occur on Day 0 and assessments will primarily focus on maternal and fetal safety evaluations prior to dosing. Subjects will be randomly assigned to treatment on Day 1 of tThe 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 managed per the investigator's judgment.

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.

~~If a subject has not delivered by the end of treatment,~~ **Subjects who remain undelivered after 48 hours will be scheduled for** a face-to-face post-infusion assessment visit ~~will be scheduled~~ **for obstetric assessments** 1 week (± 1 week **acceptable range: 3 to 14 days**) following the Inpatient Randomized Treatment Phase ~~for maternal-fetal assessments~~ **(Note: study documents may reference this visit as the 1-week face-to-face post-infusion assessment visit)**. The subject will then be contacted every week (± 1 week) **via telephone** to determine if birth has occurred. **If the subject delivers the baby prior to the face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and liver function tests (see Table 5) and the assessments for the Delivery Phase (see Section 3.1.4) will be performed.**

~~In~~ **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. ~~A maternal post-delivery assessment~~ **During the Maternal Post-Delivery Assessment Phase, the subject** will be conducted by telephone within 6 weeks (± 2 weeks) of delivery **for a post-delivery assessment.**

During the Neonatal Medical Review Phase, ~~t~~The neonatologist subinvestigator will conduct a comprehensive review of the newborn's ~~birth hospitalization~~ **medical** records, including any admission to an intensive or specialized care unit and any hospital readmission or outpatient surgery, ~~following discharge from an acute care setting~~ **from delivery** through 28 days EDD, where EDD is defined as 40^{0/7} weeks' gestation for all subjects.

The subject or other legal guardian for the infant (~~both delivered and undelivered~~) will **also** be asked to consent to participate in a **separate** long-term study to follow infants for safety and neurodevelopmental 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 face-to-face post-infusion assessment visit. (Note: In France, consent for the infant study is required during the Screening Phase, see Section 4.2 [inclusion criterion 1] and Section 3.1.1).**

An interim analysis will occur after 130 ~~mother/infant pairs~~ **subjects have completed delivery and have time-to-delivery results available** ~~all assessments~~. At the interim analysis, all available safety and efficacy data will be reviewed by an unblinded independent data monitoring committee who may make recommendations to terminate the study.

Protocol Summary, Study Endpoints/Assessments

The following are the key secondary efficacy endpoints:

- **Retosiban clearance and volume of distribution and the effect of covariates on these parameters**

The following are the safety endpoints (maternal, fetal, and neonatal, as appropriate):

- Edinburgh Postnatal Depression Scale
- ~~Follow-up amniotic fluid index determined by abdominal ultrasound~~
- Fetal acidosis
- AEs of special interest
 - Neonatal
 - Intraventricular hemorrhage/periventricular leukomalacia **with cysts or porencephaly**
 - Neonatal **Necrotizing** enterocolitis (**any modified Bell's staging criteria**)

Section 1.1., 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. . . .

Section 1.2., Rationale

This study (**ZINN**) is designed to test this hypothesis through a direct comparison with atosiban, a mixed oxytocin vasopressin antagonist indicated for short-term use to delay imminent preterm birth in women between 24^{0/7} and 33^{6/7} weeks' gestation in preterm labor.

Section 1.3., Benefit:Risk Assessment

Summaries of findings from both clinical and nonclinical studies conducted with GSK221149 can be found in the IB [**GlaxoSmithKline** ~~GSK~~ Document Number CM2006/00201/03**5**]. ~~The following section~~ **Table 1 and Table 2** outlines the risk assessment and mitigation strategy for this protocol.

Table 1 Potential Risks of Clinical Significance

Retosiban [e.g., GSK221149]		
Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Fetal exposure through placental transfer	<p><u>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.</u></p> <p><u>The p</u>Preclinical data indicate very minimal, if any, maternal CNS penetration or placental transfer of retosiban as supported by the following:</p> <ul style="list-style-type: none"> 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). <p>Retosiban is a substrate of P-glycoprotein 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.</p> <p>¶ In reproductive toxicology studies in pregnant monkeys, <u>where retosiban was given to pregnant monkeys</u>, there were no adverse mother and <u>or</u> infant behavioral or locomotor effects observed that were suggestive of CNS toxicity.</p> <p>¶ In rodent neurobehavioral safety studies, there were no adverse clinical signs observed at doses up to 1000 mg/kg.</p> <p><u>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.</u></p> <p><u>The short half-life of retosiban (~2 hours) is expected to minimize any significant risk.</u></p>	<p>Analysis of mMaternal blood and cord blood samples will be performed <u>analyzed</u> to test for levels of retosiban in women who deliver at an investigative center within 12 hours of the completion <u>or discontinuation</u> of <u>the</u> study treatment infusion in this study.</p> <p>Surveillance for signals indicating adverse fetal or neonatal effects with in utero exposure to retosiban will be performed throughout this study.</p> <p>Infants exposed to retosiban in utero will be followed for a minimum of 24 months <u>5 years</u> in a separate follow-up study to assess <u>overall</u> safety and neurodevelopmental outcomes.</p> <p><u>Unblinded safety data will be monitored by an IDMC.</u></p>

Retosiban [e.g., GSK221149]		
Potential Risk of Clinical Significance	<u>Summary of Data / Rationale for Risk</u>	Mitigation Strategy
Neonatal exposure via breast milk	<p><u>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.</u></p> <p>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 <u>the end of the infusion treatment</u>. 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.</p>	<p>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.</p> <p>¶ When breast milk/colostrum is produced prior to 4 hours from receiving <u>of the completion or discontinuation of the</u> study treatment, a sample will be collected for evaluation, and consumption by the baby is not permitted.</p> <p>¶ When breast milk/colostrum is produced between 4 and 12 hours from receiving <u>of the completion or discontinuation of the</u> 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 receiving <u>of the completion or discontinuation of the</u> study treatment.</p> <p>¶ When breast milk is produced more than 12 hours after <u>the completion or discontinuation of the</u> receiving 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.</p> <p><u>Safety monitoring for signals indicating adverse effects in infants following exposure to retosiban via breastfeeding will be performed throughout the study.</u></p> <p><u>Unblinded safety data will be monitored by an IDMC, including infants exposed to retosiban via breastfeeding.</u></p>

Retosiban [e.g., GSK221149]		
Potential Risk of Clinical Significance	<u>Summary of Data / Rationale for Risk</u>	Mitigation Strategy
Uterine atony and postpartum hemorrhage due to oxytocin receptor antagonism	<p>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.</p> <p><u>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.</u></p> <p><u>The available clinical data for other oxytocin antagonists suggest the adverse effects of atony and postpartum hemorrhage are limited [Valenzuela, 1995; Thornton, 2009].</u></p> <p>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.</p> <p>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:</p> <ul style="list-style-type: none"> • 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 <u>discontinuation of retosiban.</u> <p><u>The incidence of primary postpartum hemorrhage (within 24 hours of delivery) is estimated to be between 4% to 6% of mothers who delivered [ACOG, 2006].</u></p>	<p>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.</p> <p>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.</p> <p>Retained placenta and postpartum hemorrhage are AEs of special interest requiring the collection/assessment of risk factors for <u>postpartum hemorrhage</u>, eCRFs for any event of <u>postpartum hemorrhage</u>, and clinical parameters related to <u>postpartum hemorrhage</u>. Evaluations will include outcomes such as time from delivery to expulsion of placenta and estimated blood loss.</p> <p><u>Unblinded safety data will be monitored by an IDMC.</u></p>

Retosiban [e.g., GSK221149]		
Potential Risk of Clinical Significance	<u>Summary of Data / Rationale for Risk</u>	Mitigation Strategy
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].	<p>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.</p> <p>Placental tissue samples will be collected in this study (200721 [ZINN]) when delivery occurs at an investigative center to examine safety and efficacy outcomes in subjects with subclinical intrauterine infection based on histopathologic examination by a central laboratory.</p> <p>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 on 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.</p>
Potential drug-drug interaction with i nhibitors of BCRP or P-gp	<p>Retosiban is a substrate of murine BCRP and P-gp <i>in vitro</i>.</p> <p>Inhibitors of BCRP and P-gp have the potential to increase exposure of retosiban when co-administered.</p> <p>BCRP and P-gp is are 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.</p> <p>Clinical experience with exposures 10-fold higher than the exposure at the planned therapeutic dose have shown retosiban to be safe and well tolerated, with no observed untoward effects in adult women of childbearing potential.</p>	<p>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.</p> <p>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.</p>

Retosiban [e.g., GSK221149]		
Potential Risk of Clinical Significance	<u>Summary of Data / Rationale for Risk</u>	Mitigation Strategy
<u>Potential drug-drug interaction: Increased exposure of retosiban when co-administered with inhibitors of CYP3A4</u>	<u>In a clinical study with healthy subjects, co-administration of retosiban with ketoconazole (a strong CYP3A4 inhibitor) increased the C_{max} and AUC of retosiban, 5.2- and 8.7 fold, respectively.</u>	<u>Administration of strong CYP3A4 inhibitors concomitantly with IP requires an adjustment to the retosiban dosing regimen (see Section 5.1.1.1 and the IB). Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure.</u>
<u>Potential drug-drug interaction: Decreased exposure of retosiban when co-administered with inducers of CYP3A4</u>	<u>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%.</u>	<u>Administration of strong CYP3A4 inducers concomitantly with IP requires an adjustment to the retosiban dosing regimen (see Section 5.1.1.1 and the IB). Retosiban will only be given for 48 hours, limiting both maternal and fetal exposure.</u>
<u>Potential decreased therapeutic effect of drugs metabolized by CYP3A4 when co-administered with retosiban</u>	<u>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.</u>	<u>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.</u>

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

Table 2 **Potential Safety Concerns**

<u>Potential Safety Concerns</u>	<u>Summary of Data / Rationale for Concern</u>	<u>Mitigation Strategy</u>
<u>Pulmonary edema</u>	<p><u>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.</u></p> <p><u>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].</u></p>	<p><u>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.</u></p> <p><u>Combination administration of a tocolytic is not permitted in the clinical studies.</u></p> <p><u>Maintenance tocolysis is not allowed.</u></p> <p><u>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.</u></p>

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

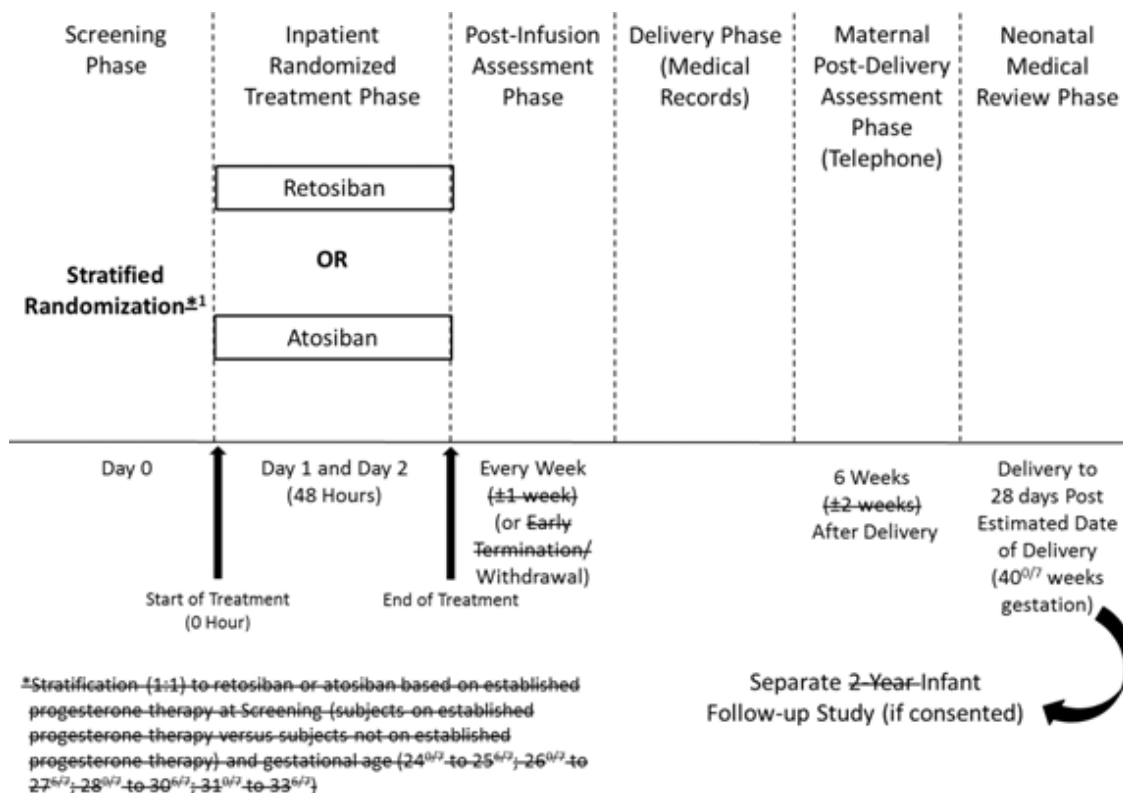
Section 3.1., Study Design

This **ZINN** is a Phase III, randomized, double-blind, double-dummy, multicenter study. This study will be conducted in approximately 330 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.

Prior to randomization, each subject will be stratified by progesterone treatment and GA determined by (1) known fertilization date, either *in vitro* fertilization or intrauterine insemination; or (2) ~~last menstrual period~~ **a best estimated due date** confirmed or established by the earliest ultrasound prior to 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.~~ 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}.

The study **ZINN** will consist of 6 phases: Screening, Inpatient Randomized Treatment, Post-Infusion Assessment, Delivery Phase (Medical Records), Maternal Post-Delivery Assessment Phase (Telephone), and Neonatal Medical Review Phase (see schematic). The duration of any 1 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 atosiban 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. Subjects who have not delivered after 48 hours will return for a face-to-face post-infusion assessment 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 atosiban) is allowed.

The Screening Phase will occur on Day 0 and assessments will primarily focus on maternal and fetal safety evaluations prior to dosing. 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 managed per the investigator's judgment. Subjects who do not experience labor progression and remain undelivered after 48 hours will be managed per the investigator's judgment. For Subjects who remain undelivered subjects, after 48 hours will be scheduled for a face-to-face post-infusion assessment visit will be scheduled for maternal-fetal for obstetric assessments 1 week (±1 week acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase (Note: study documents may reference this visit as the 1-week face-to-face post-infusion assessment visit). The subject will then be contacted every week (±1 week) via telephone to determine if birth has occurred. If the subject delivers the baby prior to the face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and liver function tests (see Table 5) and the assessments for the Delivery Phase (see Section 3.1.4) will be performed.

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. For those subjects who deliver at the investigative center, a placental tissue sample will be obtained at the time of delivery for central histopathology examination and a cord blood sample will be collected for potential genetic research and biomarker assays; if, If delivery occurs within 12 hours of investigational product (IP) (retosiban or atosiban) completion or discontinuation, the cord blood samples will also be used for the pharmacokinetic (PK) assessment, and, if required, a corresponding maternal blood sample will be collected for PK analysis (see Section 6.5.1). 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. A maternal post-delivery assessment will be conducted by telephone within 6 weeks (±2 weeks) of delivery.

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) and the EO-5D-5L (-2 weeks/+6 weeks).

During the Neonatal Medical Review Phase, ~~t~~The neonatologist subinvestigator will conduct a comprehensive review of the newborn's medical records, including any admission to an intensive or specialized care unit and any hospital readmission or

outpatient surgery, following discharge from an acute care setting from delivery through 28 days EDD, where EDD is defined as 40^{0/7} weeks' gestation for all subjects.

The ~~parent/~~ **subject or other** legal guardian of the infant will also be asked to provide consent **to participate in** for a separate infant follow-up study to assess 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 face-to-face post-infusion assessment visit (Note: In France, consent for the infant study is required during the Screening Phase, see Section 4.2 [inclusion criterion 1] and Section 3.1.1).**

An interim analysis will occur after 130 ~~mother/infant pairs~~ **subjects have** completed **delivery and have time-to-delivery results available** all assessments. At the interim analysis, all available safety and efficacy data will be reviewed by an unblinded independent data monitoring committee (IDMC) who may make recommendations to terminate the study (see Section 9.8). Details of the interim analysis are provided in Section 8.3.4. Subjects will continue to be enrolled while the interim analysis is being conducted.

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~~ **based on (1) a clinically relevant reduction in the of contraction frequency of contractions without an increase in and/or intensity or (2) no change in the cervical dilation 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 **(for details see Table 3). Investigators will be required to indicate in the electronic case report form (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 response. The duration of the treatment should not exceed 48 hours and the total dose should not exceed 582 mg.

Randomized treatment can be discontinued as outlined in Section 4.4.2. Subjects discontinuing randomized treatment will be managed according to the standard care and asked to remain on study through the Maternal Post-Delivery Assessment Phase. These subjects will also be asked to consent to the infant follow-up study, **with the exception of subjects in France (see Section 4.2 and Section 3.1.1).**

Section 3.1.1., Screening Phase

However, 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 the consent having been signed. **Additionally, in France, subjects providing consent to participate in ZINN at Screening must also provide signed and dated written consent for their infant to participate in the infant**

follow-up study (200722 [ARIOS]) (see Section 4.2).

The GA will be determined by (1) known fertilization date, either *in vitro* fertilization or intrauterine insemination; **or** (2) ~~last menstrual period~~ **a best estimated due date** confirmed **or established** by the earliest ultrasound **performed** prior to 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 ~~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~~ **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.

Section 3.1.2.1., Before Treatment

Prior to dosing, the investigators must confirm the fetal heart rate **pattern** remains reassuring, the uterine contraction rate is not less than 4 contractions over a 30-minute interval, and the electrocardiogram (ECG) does not have clinically significant abnormalities (see Section 6.1).

Section 3.1.2.3., End of Treatment

~~If not already obtained, t~~ **The subject or other legal guardian for the infant (both delivered and undelivered) will be asked to consent to participate in a separate long-term infant follow-up study for safety and neurodevelopment. if not already obtained. Note: In France, consent for the infant study is required during the Screening Phase (see Section 4.2 and Section 3.1.1).**

The study site staff will schedule the face-to-face post-infusion assessment visit for ~~maternal-fetal~~ **obstetric** assessments 1 week (± 1 week **acceptable range: 3 to 14 days**) after the end of treatment (see Section 3.1.3).

If the subject delivers the baby prior to the ~~outpatient~~ **face-to-face post-infusion assessment** visit, **central laboratory assessments for hematology, chemistry, and liver function tests (see Table 5)** and the assessments in Section 3.1.4 will be **performed** followed.

Section 3.1.3., Post-Infusion Assessment Phase

~~For s~~ **Subjects who have not delivered, the subject remain undelivered after 48 hours will return be scheduled** for a face-to-face post-infusion assessment visit for ~~maternal-~~

~~fetal~~ **obstetric** assessments **as part of the Post-Infusion Assessment Phase. The visit will be scheduled** 1 week (~~± 1 week~~ **acceptable range: 3 to 14 days**) following her release from the acute care setting per the investigator's judgment **Inpatient Randomized Treatment Phase. See Section 3.1.2.3 for details on required assessments when the baby is delivered before the face-to-face post-infusion assessment visit.**

The subject will then be contacted every week (~~± 1 week~~) via telephone to determine if she has delivered (see Section 3.1.4 **for a summary of assessments performed at delivery**). Note: This assessment should be completed remotely (by telephone); however, 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 a telephone assessment is due, this assessment may be completed face-to-face.

Section 3.1.4., Delivery Phase

For subjects who deliver at the investigative center, a placental tissue sample will be obtained at the time of delivery for central histopathologic examination and a cord blood sample will be collected for potential genetic research and biomarker assays; ~~if~~ **If** delivery occurs within 12 hours of IP completion or discontinuation, the **cord** blood samples will also be used for the PK assessment (see SPM for information about how these samples will be collected). **and, if required, a corresponding maternal blood sample will be collected for PK analysis (see Section 6.5.1).** In addition, ~~if~~ **a breast milk/colostrum sample will be collected for PK analysis in women who deliver at the** delivery was **investigative center and produce breast milk** within 12 hours of ~~after~~ **after** IP completion or discontinuation, ~~a sample of breast milk/colostrum will be obtained if lactogenesis has occurred~~ (see Section 6.5.3).

Section 3.1.5., Maternal Post-Delivery Assessment Phase

The subject will be contacted via telephone for the Maternal Post-Delivery Assessment Phase to be conducted within 6 weeks (~~± 2 weeks~~) following delivery. Maternal assessments conducted at this contact will include the following:

- Review of concomitant medications and medical/obstetric history (**± 2 weeks**)
- Recording of AEs and SAEs (maternal) (**± 2 weeks**)
- Recording of AEs and SAEs of neonate if discharged from hospital and through 28 days post EDD (**± 2 weeks**)
- Status of breastfeeding (**± 2 weeks**)

- Postnatal administration of the Edinburgh Postnatal Depression Scale (EPDS) and the EuroQol 5-dimensional 5-level (EQ-5D-5L) questionnaire **(-2 weeks/+6 weeks)**
- Assessment of postpartum bleeding **(±2 weeks)**

~~If not already obtained, t~~The subject or other legal guardian will be asked to provide consent for the infant (whether delivered or undelivered) to participate in a separate infant follow-up study for safety and neurodevelopment, **if not already obtained. Note: In France, consent for the infant study is required during the Screening Phase (see Section 4.2 and Section 3.1.1).**

Section 3.2.1.1., 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 treatment response is defined as **based on (1) a clinically relevant reduction in the of contraction frequency of contractions without an increase in and/or intensity or (2) no change in the cervical dilation 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, 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 **(for details see Table 3).**

Section 3.2.2., Study Population

Pregnant adolescents aged 12 to 17 years are included based on prior discussions with regulatory agencies, **unless national or local regulations restrict the age for study enrollment to subjects 18 to 45 years (see Section 4.2).**

Section 4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK IP or other study treatment that may impact subject eligibility is provided in the IB and IB supplement(s) [GlaxoSmithKline Document Number CM2006/00201/05], the package insert for atosiban [Tractocile SmPC, 2013], and other pertinent documents.

1. Signed and dated written informed consent is required prior to a subject's participation in the study **Study 200721 (ZINN)** and the performance of any protocol-specific procedures. **At sites where enrollment of adolescents is allowed, a** 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.

French Subjects: Participation in Study 200721 (ZINN) also requires that the subject provide signed and dated written consent for her infant to participate in Study 200722 (ARIOS), a follow-up study assessing long-term safety and outcomes in infants born to mothers participating in retosiban treatment studies.

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 labor (Note: This protocol includes pregnant adolescents, aged 12 to 17 years, as appropriate, **unless based on national or local regulations restrict the age for study enrollment to subjects aged 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) ~~last menstrual period~~ **a best estimated due date**-confirmed **or established by** the earliest ultrasound prior to 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 ~~a 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~~ **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. ~~Subjects~~**Females** must be diagnosed with preterm labor according to both of the following ~~criteria~~ **(a or 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
- ii. If < 2 cm dilation by **the required initial** digital cervical examination, a cervical change **(2 examinations must be documented) consistent of an increase of at least 25% effacement or 1 cm dilation 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**
 - **A 1-cm increase in cervical dilation by digital cervical examination**

Section 4.3., 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, 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 urine drug screen findings suggestive **positive for** of substance abuse that may either be implicated as the cause of preterm labor (e.g., abuse of cocaine, **phencyclidine (PCP)**, or methamphetamines, **or amphetamine**) or have the potential to complicate the pregnancy outcome (e.g., alcohol abuse or opioid addiction)
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 positive findings for substances other than cocaine, PCP, methamphetamine, or amphetamine is at the investigator's discretion (examples include alcohol, cannabinoids, and opiates)**
910. 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
142. Women with documented active hepatitis B or hepatitis C viral infection, unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

123. History of sensitivity to the IPs or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK/PPD medical monitor, contraindicates their participation.

Section 4.4., Withdrawal Criteria **From Study and Discontinuation of IP**

The section describes and distinguishes the following:

- **Withdrawal of the subject from the study after randomization but before administration of IP (Section 4.4.1.1) and after administration of IP (Section 4.4.1.2)**
- **Discontinuation of the IP (Section 4.4.2), 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.**

Section 4.4.1.1., 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 ECG cannot be dosed- **and should 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.

Dosing may be started before local liver function test results are available; however, if local laboratory results are available before the start of dosing and ALT is $>2 \times$ the upper limit of normal (ULN) or bilirubin is $>1.5 \times$ ULN ($>35\%$ direct bilirubin), the subject should not be dosed and should be withdrawn from the study. **An isolated bilirubin $>1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin is $<35\%$.** See Section 6.3.1 for liver stopping criteria for management of abnormal test results that become available after the start of dosing.

Section 4.4.1.2., 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 GSK/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 after starting the Inpatient Randomized Treatment Phase and before the Post-Infusion Assessment Phase will be asked to return and complete the assessments specified for the **face-to-face** post-infusion **assessment** visit **before withdrawing from the study** (see Section 3.1.3 and Table 3.5). If the subject withdraws after the face-to-face post-infusion **assessment** visit, the investigator will attempt to contact the subject by telephone to determine if she has delivered and to gather the information specified in Section 3.1.4.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also 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 based on previous noncompliance.

In cases where the **subject is deemed “Lost to Follow-up” (e.g., subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit)**, the **site investigator or designee** should 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**) ~~so that they can appropriately be withdrawn from the study.~~ These contact attempts should be documented in the subject’s medical record. Should the subject continue to be unreachable, then and only then will he/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.

Section 4.4.2., 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.

The investigator should consult the PPD medical monitor prior to discontinuing any subject from the IP based on urine drug screen results that become available after the IP has been initiated.

~~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.

5. An abnormal corrected QT interval using 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 \geq 530 msec in a subject with a baseline QTcF value between 450 and 480 msec

6. Abnormal liver function test result detected during standard care of the subject based on **the criteria detailed in Section 6.3.1** the following criteria:

- ~~ALT \geq 3 \times ULN and bilirubin \geq 2 \times ULN (>35% direct bilirubin)~~
- ~~ALT \geq 8 \times ULN~~
- ~~ALT \geq 3 \times ULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia)~~

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

Subjects discontinuing the IP who have not yet delivered will continue in the study through delivery and the maternal post-delivery assessment. 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. **Note: In France, consent for the infant study is required during the Screening Phase (see Section 4.2 and Section 3.1.1).**

Section 4.5.. Subject and Study Completion

A completed subject is defined as one who has completed all phases of the study (see Section 3.1 and Table 5). 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 4.4.2).

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.

Section 5.1., Investigational Product and Other Study Treatment

Table 3 Retosiban Investigational Product and Other Study Treatment

Product Name	Retosiban Solution for Infusion	PTM IV Solution (0.9% NaCl)
...		
Dosing instructions:	<p>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.</p> <p>An adequate treatment response is defined as a based on (1) clinically relevant reduction in the 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 of contractions without an increase in cervical dilation.</p> <p>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. 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.</p> <p>For subjects receiving concomitant treatment with a potent 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.</p>	<p>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.</p> <p>An adequate treatment response is defined as a based on (1) clinically relevant reduction in the 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 of contractions without an increase in cervical dilation.</p> <p>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. 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.</p> <p>For subjects receiving concomitant treatment with a potent 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.</p> <p>For subjects receiving concomitant treatment with a 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</p>

Product Name	Retosiban Solution for Infusion	PTM IV Solution (0.9% NaCl)
	<p>For subjects receiving concomitant treatment with a 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.</p> <p><u>A list of strong, moderate, and weak CYP3A4 inhibitors and inducers is provided in Appendix 3.</u> See the Study Pharmacy Manual for detailed instructions.</p>	<p>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.</p> <p><u>A list of strong, moderate, and weak CYP3A4 inhibitors and inducers is provided in Appendix 3.</u> See Study Pharmacy Manual for detailed instructions.</p>

CYP3A4 = cytochrome P450 3A4 enzyme; **eCRF = electronic case report form**; IV = intravenous; GSK = GlaxoSmithKline; NaCl = sodium chloride; PTM = placebo to match.

Table 4 Atosiban Investigational Product and Other Study Treatment

Product Name	Atosiban Solution for Injection and Atosiban Solution for Infusion	PTM IV Solution (0.9% NaCl)
...		
Preparation instructions	<p>Withdraw 0.9 mL of a 0.9 mL labeled vial of atosiban 6.75 mg/0.9 mL solution for injection into a syringe. Label the syringe with the protocol number, subject number, infusion rate, and dosing session number.</p> <p>Withdraw 4025-mL solution from a 400250- mL 0.9% NaCl infusion bag and discard the solution. Replace the solution with 4025 mL of atosiban 7.5 mg/mL concentrate solution for infusion from two <u>five</u> 5 mL vials to obtain a concentration of <u>0.75 mg/mL (187.5 mg</u> atosiban in 400250 mL. <u>0.9% NaCl (0.75 mg/mL)</u>. The reconstituted product is a clear, colorless solution without particles.</p> <p>Label the IV bag with protocol number, subject number, infusion rate, and dosing session number.</p> <p>Prepare new 400250-mL bags in the same manner as described to allow the infusion to be continued. If an infusion bag with a different volume is used, a proportional calculation should be made for the preparation.</p> <p>Once the vial has been opened, the dilution must be performed immediately. Diluted solution for IV administration should be used within 24 hours after preparation.</p> <p>See the Study Pharmacy Manual for detailed instructions.</p>	<p>Withdraw 0.9 mL of 0.9% NaCl solution for injection into a syringe. Label the syringe with the protocol number, subject number, infusion rate, and dosing session number.</p> <p>The placebo admixture for continuous infusion will consist of a 0.9% NaCl infusion bag, labeled with the protocol number, subject number, infusion rate, and dosing session number.</p> <p>The volume of the 0.9% NaCl infusion bag should be matched to the 0.9% NaCl infusion bag volume used for the atosiban admixture.</p> <p>See Study Pharmacy Manual for detailed instructions</p>

Section 5.1.1.1., Retosiban

A list of strong, moderate, and weak CYP3A4 inhibitors and inducers is provided in Appendix 3.

Section 5.2., Managing Dose Interruptions

Temporary interruptions of the IP are permitted. The following procedures should be followed in the event of a retosiban 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.**

For atosiban dose interruptions, resume the infusion at the same rate that was used before the dose interruption.

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

Section 5.23., Treatment Assignment

Subjects within each stratum will be randomly assigned in 1:1 ratio to receive either retosiban or atosiban using an interactive voice response system **(IVRS)/interactive web response system (IWRS)** in accordance with the randomization schedule.

Section 5.34., Blinding

The principal investigator **or treating physician** may unblind a subject's treatment assignment **only** 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).

The principal ~~It is preferred (but not required) that the~~ investigator must first **contact** discuss options with the GSK/PPD medical monitor ~~or appropriate GSK/PPD study personnel~~ **to discuss options** before unblinding the subject's treatment assignment. The PPD medical monitor will authorize the unblinding, and the treatment assignment will be provided. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

The PPD medical monitor may unblind the treatment assignment after discussing the rationale for unblinding with the principal investigator. However, in the event of an emergency, when it is not possible to contact the medical monitor, the investigator may contact the interactive voice response system and obtain subject-specific randomization information. Notification of unblinding will be sent to GSK, PPD, and the study center.

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.

Section 5.78., 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	5.78.1.5.,	Strong	CYP3A4	Inhibitors.
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A list of strong, moderate, and weak CYP3A4 inhibitors is provided in Appendix 3.

Section	5.78.1.6.,	Strong	CYP3A4	Inducers.
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A list of strong, moderate, and weak CYP3A4 inducers is provided in Appendix 3.

Section 5.78.2., Prohibited Medications and Nondrug Therapies

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.

Table 35 Time and Events Table

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ¹²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	<u>Withdrawal From Study</u>
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Every week (±1 week) (or early termination/withdrawal) <u>Face-to-face post-infusion visit</u>	<u>Weekly post-infusion telephone call</u>	Information collected via medical records review	6 weeks (±2 weeks) after delivery ³	Delivery to 28 days post EDD	
Clinical and Other Assessments										
Written informed consent and medical releases for treatment ²⁴	X									
<u>Discuss and request</u> cConsent for participation in the infant follow-up study ⁵		X ⁵ ←————→ X								<u>X</u>
Inclusion/exclusion criteria confirmation	X			<u>X</u>						
Subject demography	X									
Medical history (including obstetrics history ³) ⁶	X				X		X	X		
Urine drug screen ⁴⁷	X			X						
Physical examination (including <u>height and weight</u>)	X									

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ¹²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	<u>Withdrawal From Study</u>
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Every week (±1 week) (or early termination/ withdrawal) <u>Face-to-face post-infusion visit</u>	<u>Weekly post-infusion telephone call</u>	Information collected via medical records review	6 weeks (±2 weeks) after delivery ³	Delivery to 28 days post EDD	
Cervical dilation based on digital examination ⁵⁸	X	X	X	X	X					
Estimated fetal weight <u>and head circumference</u> via ultrasound	X									
Determine AFI via ultrasound ⁶⁹	X	X								
Uterine contractions ⁷¹⁰	X									
Schedule <u>face-to-face</u> post-infusion <u>assessment</u> visit			X							
Investigational Products⁸¹¹										
Investigational product (retosiban or atosiban)		X	X							

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ¹²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Every week (±1 week) (or early termination/ withdrawal) <u>Face-to-face post-infusion visit</u>	<u>Weekly post-infusion telephone call</u>	Information collected via medical records review	6 weeks (±2 weeks) after delivery ³	Delivery to 28 days post EDD	
Efficacy Assessments										
Date and time of delivery							X ⁹¹²			
Mode of delivery							X ⁹¹²			
Indication for delivery							X ⁹¹²			
<u>Neonatal composite outcomes</u>									X	
<u>Neonatal hospital stay</u>									X	
Maternal Safety Assessments										
Concomitant medications			X					X		X
ECG 12-lead ¹⁰¹³	X									
Vital sign measurements (BP, pulse rate, <u>respiratory rate</u> , and temperature) ¹¹¹⁴	X	X	X		X					
AEs ₁ , SAEs ₂ , and DREs: maternal			X					X		X
Breastfeeding status								X		

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ¹²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	<u>Withdrawal From Study</u>
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Every week (±1 week) (or early termination/ withdrawal) <u>Face-to-face post-infusion visit</u>	<u>Weekly post-infusion telephone call</u>	Information collected via medical records review	6 weeks (±2 weeks) after delivery ³	Delivery to 28 days post EDD	
Edinburgh Postnatal Depression Scale ¹²¹⁵ (maternal)								X		
<u>Local laboratory assessments (LFTs only)</u> ¹⁶	X			X						
Central laboratory assessments (including hematology, chemistry, and LFTs) ¹³¹⁷	X		X	X	X ¹⁷					
<u>Local laboratory assessments (LFTs only)</u> ¹³	X			X						
Physical examination (brief)					X					
Status of postpartum bleeding								X		
Fetal Safety Assessments										
<u>Electronic fetal heart rate monitoring</u> ¹⁴	X ¹⁸	X ¹⁹	X ¹⁹	X ¹⁹	X ²⁰		X ²¹			
<u>AEs, SAEs, and DREs: fetal</u>			X				X			

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ¹²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Every week (±1 week) (or early termination/ withdrawal) <u>Face-to-face post-infusion visit</u>	<u>Weekly post-infusion telephone call</u>	Information collected via medical records review	6 weeks (±2 weeks) after delivery ³	Delivery to 28 days post EDD	
Neonatal Safety Assessments										
AEs ₁ , SAEs, and DREs: neonatal							X		X	
Neonatal Apgar Scores (1 and 5 minutes)							X ^{7,12}			
Neonatal growth parameters							X ^{7,12}			
Neonatal blood gases							X ^{7,12}			
Health Outcome Assessments										
Maternal and neonatal health care resource use ^{15,22}							X		X	
EQ-5D-5L (maternal)		X						X ³		
Pharmacokinetic Assessments										
Maternal PK blood sample ^{16,23}		X ^{16,23}	X ^{16,23}							
Cord blood sample ^{17,24}							X			
Breast milk/colostrum sample ^{18,25}							X			
Histopathology										
Placental tissue sample ^{19,26}							X			

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ¹²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Every week (±1 week) (or early termination/ withdrawal) <u>Face-to-face post-infusion visit</u>	<u>Weekly post-infusion telephone call</u>	Information collected via medical records review	6 weeks (±2 weeks) after delivery ³	Delivery to 28 days post EDD	
Biomarker Assessments										
Genetic research maternal blood sample for maternal DNA ²⁰²⁷	X									
Fetal fibronectin (optional) ²¹	X									
<u>Blood sample for maternal inflammation biomarker</u>	X									
Biomarker and genetic cord blood sample ²²²⁸							X			
Other Assessments										
<u>Fetal fibronectin (optional)</u> ²¹²⁷	X			X						
Cervical length via transvaginal ultrasound (optional) ²³³⁰	X			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; **EPDS = Edinburgh Postnatal Depression Scale**; EQ-5D-5L = EuroQol 5-dimensional 5-level questionnaire; **IP = investigational product**; LFT = liver function test; PK = pharmacokinetic; SAE = serious adverse event; **ULN = upper limit of normal**.

1. For undelivered subjects who are subsequently diagnosed with recurrent preterm labor 24 hours or more following completion of the Inpatient Randomized Treatment Phase, retreatment with blinded IP is permitted at the discretion of the investigator (see Section 3.1.3.1).

42. Subjects who remain undelivered after 48 hours Conducted when subject is discharged from an acute care setting, either to home or to a nonacute care setting; the subject will return for a face-to-face post-infusion assessment visit for maternal-fetal **obstetric** assessments 1 week (±1 week **acceptable range: 3 to 14 days**) following the **Inpatient**

- Randomized Treatment Phase** her release from the acute care setting. (Note: study documents may reference this visit as the 1-week face-to-face post-infusion assessment visit). The subject will then be contacted every week (± 1 week) via telephone to determine 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. **If the subject delivers the baby prior to the face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and LFTs and the assessments for the Delivery Phase (see Section 3.1.4) will be performed.**
3. **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) and the EQ-5D-5L (-2 weeks/+6 weeks) (see Section 3.1.5 for list of assessments and visit windows).**
 24. 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.
 5. **The subject or other legal guardian for the infant will be asked to consent to participate in a separate long-term study to follow infants for safety and neurodevelopment outcomes. The subject or other legal guardian for the infant (both delivered and undelivered) will be asked to give consent for the infant follow-up study at any time during the study that is appropriate and convenient. (Note: In France, consent for the infant study is required during the Screening Phase [see Section 4.2 and Section 3.1.1]). Withdrawal from the study after beginning randomized treatment or discontinuing IP does not preclude involvement in the infant follow-up study.**
 36. **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.**
 47. The urine drug screen will be performed locally using a point-of-care, qualitative testing device.
 58. 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.
 69. The abdominal ultrasound for determination of the AFI will be performed at Screening ~~and within 12 hours of study treatment for all subjects.~~
 710. Uterine tocography **or manual palpation (if necessary)** will be performed prior to dosing to confirm the uterine contraction 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.**
 811. Antenatal corticosteroid treatment should be administered in accordance with national, society, or institutional guidelines. Magnesium sulfate for fetal neuroprotection can be given at the discretion of the investigator.
 912. Information regarding delivery will be obtained through a review of the hospital and medical records. **Growth parameters include neonatal weight, length, and head circumference.**
 103. 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.
 144. **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, All vital signs will be assessed and recorded within the following windows relative to the start of the infusion: every 15 to 30 minutes, 4 to 8 hours, and 20 to 24 hours after the start of the infusion, at the time of any dose changes,**

- at the end of the infusion, **at the time of any dose changes**, and as warranted by a medical condition or AE as part of maternal safety monitoring during the treatment phase. **It is suggested (but not required) that oxygen saturation also be assessed at Screening and recorded in source documents.**
125. **Maternal subjects will complete the Edinburgh Postnatal Depression Scale EPDS, a self-reported questionnaire, must be administered to mothers at the maternal follow-up assessment 6 weeks (~~±2 weeks~~-2 weeks/+6 weeks) after delivery.**
136. The LFTs should be ordered from the local laboratory **to confirm that ALT is not $\geq 2 \times$ ULN OR total bilirubin is not $>1.5 \times$ ULN ($>35\%$ direct bilirubin) before dosing with of the investigational product IP. An isolated bilirubin $>1.5 \times$ 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 6.3.1) **if ALT or bilirubin is abnormal**. In addition, laboratory values for hematology, chemistry, and LFTs will be determined through a central laboratory. 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 post-infusion visit, central laboratory assessments for hematology, chemistry, and LFTs should be performed.**
17. **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 6.3.1). 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. 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.**
148. Prior to dosing, if the fetal heart rate **pattern** is nonreassuring, the subject cannot be dosed. Fetal heart rate monitoring will be continuous throughout the Inpatient Randomized Treatment Phase. If the subject has not delivered at the end of the Inpatient Randomized Treatment Phase, fetal heart rate monitoring will occur at the face-to-face post-infusion assessment visit.
19. **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 02 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 6.3.11.3).**
20. **If the subject has not delivered at the end of the Inpatient Randomized Treatment Phase, fetal heart rate (fetal Doppler heart rate or cardiotocography are both acceptable) 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 6.3.11.3).**
21. **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 6.3.11.3).**
4522. 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.
4623. PK samples will be taken at the following sampling windows (relative to the start of the infusion): 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 504 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. A maternal blood sample should be collected at the same time as the cord blood sample (see Section 6.5.1) if the sample time does not already coincide with one of the PK sampling windows.**
4724. In subjects who deliver at an investigative center within 12 hours following completion or discontinuation of the investigational product **IP**, the cord blood sample will also be divided for PK analysis as well as genetic (if additional consent is provided; see Appendix 1) and biomarker analyses.

~~1825.~~ 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 investigational product **IP**.

~~1926.~~ A placental tissue sample will be collected at delivery in subjects who deliver at an investigative center.

~~207.~~ A **maternal** blood sample for genetic research will only be collected from subjects who provide separate informed consent (see Appendix 1).

28. A cord blood sample will be collected in subjects who deliver at an investigative center, if additional consent is provided.

~~249.~~ Testing for fetal fibronectin will be performed only at those institutions collecting the information as routine practice.-

~~22.~~ A cord blood sample will be collected in subjects who deliver at an investigative center.

~~230.~~ Cervical length measured by transvaginal ultrasound will be captured only at those institutions collecting the information as routine practice. Cervical length will not be used to determine study eligibility.

Section 6.1., Critical Assessments Prior to Investigational Product Administration

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

- **Electronic fetal heart rate** monitoring to confirm that the fetal heart rate **pattern** remains reassuring
- Cervical examination to ensure cervical dilation **continues to** meets 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 4.2)**. **A that the 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 (see Section 4.2).**
- Liver function tests from a local laboratory to confirm that ALT is not $\geq 2 \times \text{ULN}$ OR bilirubin is not $> 1.5 \times \text{ULN}$ ($> 35\%$ direct bilirubin), **if available (see Section 6.3.1).** **An isolated bilirubin $> 1.5 \times \text{ULN}$ is acceptable if bilirubin is fractionated and direct bilirubin is $< 35\%$. Dosing may be started prior to the availability of these results.**
- 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 4.4.1).

Section 6.2., Efficacy

Collection of efficacy **endpoint data** requires a thorough review of the hospital medical records. Review of the maternal hospital record is the responsibility of the investigator obstetrician and review of the newborn hospital record is the responsibility of the subinvestigator neonatologist.

Section 6.2.1., 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.

Section 6.2.2., 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 6.2.4)**
- **Hospital length of stay**
- **Neonatal admission to a specialized care unit and length of stay**
- **Newborn hospital readmission and length of stay**
- **Ambulatory surgery**

Section 6.2.4., Key Secondary Efficacy Endpoints

- **Retosiban clearance and volume of distribution and the effect of covariates on these parameters**

Section 6.2.4., Exploratory Efficacy Endpoints

- ~~Proportion of subjects requiring increase in infusion rate~~
- ~~Proportion of subjects receiving retreatment~~
- ~~Proportion of subjects with improved health status based on the EQ-5D-5L~~

A complete list of exploratory endpoints will be provided in the reporting and analysis plan (RAP).

Section 6.3., Safety

Fetal:

- ~~Follow-up AFI determined by abdominal ultrasound~~
- Incidence of reported AEs, including SAEs
- Fetal acidosis

Neonatal:

- IVH/periventricular leukomalacia **with cysts or porencephaly**
- Necrotizing enterocolitis **(any modified Bell's staging criteria)**

Section 6.3.1., Liver Chemistry Stopping and Follow-Up Criteria

Blood ~~samples~~ draws will be **collected** ~~obtained~~ for central laboratory evaluation at Screening (~~prior to treatment,~~) during Day 2 of the randomized treatment phase, and at the face-to-face post-infusion assessment visit for additional liver function testing in order to **ensure** ~~assure~~ subject safety and to evaluate liver event etiology ~~consistent (in alignment~~ with the US Food and Drug Administration premarketing clinical liver safety guidance);

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>.

At Screening, before IP administration, **ALT and bilirubin test results** ~~liver function tests from a local laboratory, including ALT and bilirubin,~~ 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:

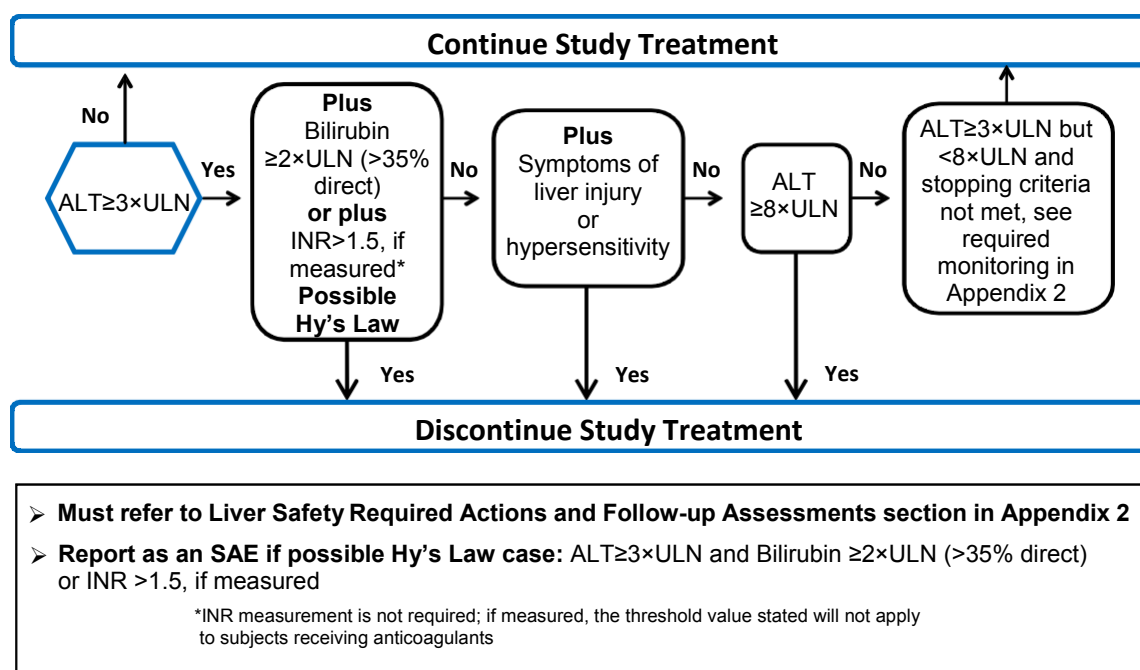
- ~~1. ALT $\geq 2 \times$ ULN OR bilirubin $> 1.5 \times$ ULN ($> 35\%$ direct bilirubin).~~ **An isolated bilirubin $> 1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin is $< 35\%$.**

Phase III-IV liver chemistry stopping criteria ~~1 to 3 are defined below and~~ are presented in **Figure 3 and** ~~a figure in~~ Appendix 2.

The local and central laboratory liver function test results should be reviewed for the abnormalities **shown in Figure 3** listed below. 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 following liver chemistry stopping criteria **shown in Figure 3 and detailed in Appendix 2**:

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

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



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.

1. ~~ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN (>35% direct bilirubin)~~
2. ~~ALT ≥ 8 × ULN~~
3. ~~ALT ≥ 3 × ULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).~~

NOTE: The central laboratory report will include results for ALT, AST, ALP, total bilirubin, and direct bilirubin.

In the event liver function test results from either the local or central laboratory reveal abnormalities consistent with the liver chemistry stopping criteria 1 to 3 listed above during the randomized treatment phase, investigators should complete the following actions:

- Immediately discontinue study treatment in the unlikely event that subject is receiving the IP
- Report the event to GSK/PPD within 24 hours of learning its occurrence (see Table 3 and Section 6.3.8)
- Complete the liver event and SAE eCRFs, where applicable (see Section 6.3.10). All events of $ALT \geq 3 \times ULN$ and bilirubin $\geq 2 \times ULN$ ($>35\%$ direct), termed “Hy’s Law,” must be reported as an SAE.
- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below
- Do not restart IP

In addition, for criterion 1, do the following:

- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, ALP, bilirubin) resolve, stabilize, or return to within baseline values

For those subjects meeting criteria 2 or 3, do the following:

- Make every reasonable attempt to have subjects return to clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up
- Monitor subjects weekly until liver chemistries (ALT, AST, ALP, bilirubin) resolve, stabilize, or return to within baseline values; criterion 3 subjects should be monitored as frequently as possible.

For those subjects with $ALT \geq 3 \times ULN$ but $<5 \times ULN$ and bilirubin $<2 \times ULN$ without hepatitis symptoms or rash and who can be monitored weekly for 4 weeks:

- Notify the GSK/PPD medical monitor within 24 hours of learning of the abnormality to discuss subject safety and determine if the subject should be excluded from the option for retreatment (see Section 3.1.3.1)
- Must return weekly for repeat liver chemistries (ALT, AST, ALP, bilirubin) until they resolve, stabilize, or return to within baseline values
- If at any time these subjects meet the liver chemistry stopping criteria, proceed with the follow up procedures as described above

- If after 4 weeks of monitoring, ALT $<3 \times$ ULN and bilirubin $<2 \times$ ULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values

For criteria 1 to 3, make every attempt to carry out the liver event follow up assessments described below:

- Viral hepatitis serology including:
 - Hepatitis A immunoglobulin M (IgM) antibody
 - Hepatitis B surface antigen and hepatitis B core antibody (IgM)
 - Hepatitis C RNA
 - Hepatitis E IgM antibody
 - Cytomegalovirus IgM antibody
 - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
- Blood samples for PK analysis will be taken at the following sampling windows (relative to the start of the infusion): 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 50 hours. Record the date/time of the PK blood sample draw and the date/time of the last dose of IP prior to blood sample draw in 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 SPM
- Serum creatine phosphokinase and lactate dehydrogenase
- Fractionate bilirubin, if total bilirubin $\geq 2 \times$ ULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia as relevant on the AE eCRF
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications eCRF
- Record alcohol use on the liver event alcohol intake eCRF

The following are required for subjects with ALT $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN ($>35\%$ direct) but are optional for other abnormal liver chemistries:

- Antinuclear antibody, antismooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies
- Serum acetaminophen adduct high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009])

- 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. NOTE: 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]
- Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease

Section 6.3.1.1., 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.

Section 6.3.2.3., 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 AE eCRFs pages ~~unless they are already captured on specifically designated~~ **in addition to the AE/SAE** eCRF pages such as those **to capture additional details** for the efficacy **safety** analyses.

Maternal, fetal, and neonatal AEs of special interest are listed in Section 6.3. **Guidelines for reporting these events are provided in Appendix 4.**

Section 6.3.4., Cardiovascular Events

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. This ~~The cardiovascular~~ information should be recorded ~~on~~ **in** the specific cardiovascular **section of the** eCRF within 1 week of **receipt of a cardiovascular event data query prompting its completion** ~~when the AE/SAE(s) are first reported.~~

Section 6.3.5., Death Events

~~This information should be recorded on the specific~~ **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 ~~first~~ reported.

Section 6.3.7.1., 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)
- ~~PPROM~~

Section 6.3.7.2., 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
 - ~~RDS~~
 - ~~Bronchopulmonary dysplasia~~
 - Apnea (severe)
 - Respiratory failure due to fatigue, hypoxia, or air leak from alveolar injury
- Cardiovascular
 - Patent ductus arteriosus
 - Bradycardia
 - ~~Hypotension~~
- Neurological
 - ~~IVH (all grades)~~
 - ~~Periventricular leukomalacia with cysts or porencephaly~~
 - Ventriculomegaly
 - Cerebellar hemorrhage
 - Hydrocephalus other than congenital
 - ~~Hypoxic ischemic encephalopathy~~
- Gastrointestinal
 - ~~Necrotizing enterocolitis (any modified Bell's staging criteria)~~
 - Gastroesophageal reflux
 - Aspiration pneumonia
- Hematologic
 - Anemia (~~severe~~)

- Vision
 - Retinopathy of prematurity (all stages)
- Auditory
 - Hearing disorder
- Other
 - Temperature instability
 - Hypoglycemia
 - Hyperbilirubinemia

Because these events (Section 6.3.7.1 and Section 6.3.7.2) 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 an SAE). These events will be recorded on the DRE page in the ~~maternal or neonatal~~ eCRFs. These DREs will be monitored by the IDMC and internal safety review committee team. *However, if one or all of the following conditions apply, then the event should be reported as an AE/SAE using the standard process, as summarized in Section 6.3.11:*

Section 6.3.8., Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

Adverse events and SAEs will be collected from the start of study treatment and until the follow up contact (see Section 6.3.10) 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.

Serious ~~AEs~~ will be collected over the same time period as stated above for AEs. ~~However, a~~Any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK **product** ~~concomitant medication~~, 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 Section 6.3.101.

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.

Section 6.3.10., 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 6.3) 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 4.4.1.2). 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 the SPM.

Section 6.3.101., Prompt Reporting of SAEs and Other Events to GSK/PPD

Table 6 Reporting of Serious Adverse Events and Other Events to GSK/PPD

ALT = alanine aminotransferase, CV = cardiovascular; DRE = ~~drug~~ **disease**-related event, eCRF = electronic case report form; GSK = GlaxoSmithKline; INR = International normalized ratio, SAE = serious adverse event, ULN = upper limit of normal.

The contact information for reporting SAEs is as follows:

Issue	<u>Latin America All Countries/Regions Contact</u>	<u>Europe/Asia Contact</u>
Serious Adverse Event Reporting	24-Hour Safety SAE Hotline: PPD [REDACTED] PPD [REDACTED] Safety SAE Fax: PPD [REDACTED] PPD [REDACTED]	Safety Hotline: PPD [REDACTED] Safety Fax: PPD [REDACTED]

Section 6.3.1+2.1., Physical Examination

An admission physical examination will include at 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 face-to-face post-infusion assessment visit, following conclusion of the treatment phase.

Section 6.3.1+2.2., Vital Sign Measurements

Blood pressure, pulse rate, **respiratory rate**, and temperature will be measured at the following time points during the study: Screening, Inpatient Randomized Treatment Phase (15 to 30 minutes, 4 to 8 hours, and 20 to 24 hours after the start of the infusion, at the time of any dose changes, at the end of the infusion, and as warranted by a medical condition or AE), and at the face-to-face post-infusion assessment visit.: **15 to 30 minutes, 4 to 8 hours, and 20 to 24 hours after the start of the infusion, at the time of any dose changes, at the end of the infusion, and as warranted by a medical condition**. Subjects may be either in a semirecumbent or seated position. **It is suggested (but not required) that oxygen saturation also be assessed at Screening and recorded in source documents.**

Section 6.3.1+2.3., **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 bolus 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 6.3.11.2). The electronic fetal heart rate tracing (paper or electronic) must be archived and retained in site records. Fetal heart rate (fetal Doppler heart rate or cardiotocography are both acceptable) will be recorded, will be monitored continuously from Screening to time of delivery or discharge from the acute care setting. 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 monitoring will also be performed at the 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, 2009] will be reported as an AE of special interest on a specified eCRF **in addition to the corresponding AE or SAE eCRF:**

Category II fetal heart rate tracings include all fetal heart rate tracings not categorized as Category I or III. Category III 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:

Section 6.3.1+2.4., 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 4.3)** and within 12 hours of study treatment for all subjects. ~~If a subject discontinues IP before the end of the treatment phase, the follow-up abdominal ultrasound for AFI determination should be performed within 4 hours of IP discontinuation. If a subject delivers or membranes rupture during IP administration and before the follow-up AFI has been completed, a follow-up abdominal ultrasound is no longer applicable, and the reason for not determining the AFI will be captured in the eCRF.~~ An abdominal ultrasound to assess fetal growth will be done at Screening (unless records are available documenting an ultrasound derived estimated fetal weight within 1 week of Screening, with the results and date of assessment recorded in the eCRF).

Section 6.3.1+2.5., Laboratory Assessments

With the exception of the above, all protocol required laboratory assessments, as defined in Table 3, must be performed by the central laboratory. **For subjects that do 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.**

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 biological samples collected over the course of the study that are directly related to the conduct and analysis of the study, including hematology and chemistry tests, liver function tests, and urine drug screening are summarized further in Appendix 5.

Section 6.3.1+2.6., 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**. Performance of a follow-up ECG after an abnormal finding will be at the discretion of the investigator.

Section 6.3.1+2.8., Maternal Depression

A score of 12+ indicates an increased probability of depression and investigators or designated study center personnel will be notified immediately **in order to follow-up with the subject to ensure safety**. Certain items in the scale also assess anxiety and will be used to assess level of anxiety. The EPDS will be administered to mothers at the maternal follow-up assessment 6 weeks (± 2 **-2 weeks/+6 weeks**) post-delivery (Table 3**5**).

Section 6.4., Health Outcomes

- Assess maternal health status (EQ-5D-5L) at time of IP administration and 6 weeks (± 2 **-2 weeks/+6 weeks**) after delivery

Section 6.4.1.2., Maternal Subject Reported Health Assessments

This information can be used as a quantitative measure of health as judged by the individual respondents. The EQ-5D-5L will be administered to mothers early in the drug delivery phase (while the mother is still in active preterm labor) and at the maternal follow-up assessment 6 weeks (± 2 **-2 weeks/+6 weeks**) after delivery (Table 3**5**).

Section 6.5., 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-DMPPK **Drug Metabolism and Pharmacokinetics**/Scinovo, the details of which are included in the SPM. Concentrations of retosiban will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SPM).

The samples collected for PK analyses are summarized further in Appendix 5.

Section 6.5.1., Sampling

Maternal Blood samples (approximately 2 mL) 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. ~~In addition, a PK sample (approximately 2 mL) should be taken at the onset of any maternal or fetal SAE that occurs within 24 hours after the end of the infusion.~~

Additionally, a maternal blood sample should be collected at the same time as the cord blood sample (see Section 6.5.2) 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.

Section 6.5.2., Umbilical Cord Blood

For those subjects who deliver at the investigative center, a **single** cord blood sample will be collected **and divided for biomarker assays (Section 6.8) and for potential genetic research and biomarker assays (Section 6.9).** ~~If subjects deliver at the investigative center;~~ if delivery occurs within 12 hours **following** of the IP completion or discontinuation **of IP**, a **the** cord blood sample will also be used for a PK assessment **of fetal drug exposure. 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 sampling for the study.**

Samples from retosiban-treated subjects with concomitant use of inhibitors of **BCRP** ~~breast cancer resistance protein~~ or **P-gp** ~~p-glycoprotein~~ will be analyzed for drug-drug interactions. The date and time of the sample should be noted in the eCRF.

Section 6.5.3., Retosiban Levels in Breast Milk

If breast milk/colostrum is expressed within 12 hours of receiving the completion or discontinuation of the 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 ~~within~~ **prior to** 4 hours of receiving **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 from receiving 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 receiving **the completion or discontinuation of the** study treatment.

- Breast milk produced more than 12 hours after receiving **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.

Section 6.6., 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 will not be used to determine eligibility but 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.

~~Section 6.7., Biomarkers~~

~~Section 6.7.1., Fetal Fibronectin~~

~~Section 6.7.2., Other Biomarkers~~

~~Other biomarkers as measured at the screening assessment in the maternal serum (such as interleukin-6) that may predict the relationship of time to delivery or inflammation in the fetus and outcomes based on treatment may be obtained.~~ **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 maternal blood sample for biomarker research will be collected at Screening and a cord blood sample for biomarker research will be collected during the Delivery Phase.** The samples will be stored and may be analyzed ~~in the~~ **for** future for exploratory laboratory ~~biomarkers research~~.

The blood samples collected for biomarker analyses are summarized further in Appendix 5.

Section 6.98., Genetic Research

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. At Screening (Day 0), a ~~6-mL~~ maternal blood sample **for maternal DNA** will be collected **in subjects who provide informed consent** for potential genetic ~~sampling~~ **research**. In addition, for those subjects who deliver at the investigative center, a cord blood sample will also be collected for potential genetic assays.

Additional information regarding genetic research is included in Appendix 1 **and Appendix 5.**

Section 8.1., Hypotheses

The hypotheses will be tested at 5% level with a 2-sided test. 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~~ **sequential testing method** will be used to adjust for multiplicity of key secondary endpoints such that the type I error rate will be maintained at 5%. Refer to Section 8.3.5.1.2 for details of key secondary analysis.

Section 8.3.5.1.2., Secondary Analysis

Key Secondary Analysis

The key secondary analysis for this study includes 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), length of neonatal hospital stay, and composite neonatal morbidity and mortality. 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~~ **sequential testing method** 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 sequential testing examines the hypothesis testing in a prespecified order, i.e., the testing of the second secondary endpoint will be performed only if the first secondary endpoint is significant at 5%, and testing of the third secondary endpoint will be performed only if the first and second endpoints are significant at 5%. The exact order of sequential testing will be detailed in the RAP.**

Section 9.2., Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ~~ethical~~ **guiding** principles ~~that are outlined in the~~ **of the current version** of Declaration of Helsinki 2008, including, but not limited to:

Section 10., 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.

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~~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.~~

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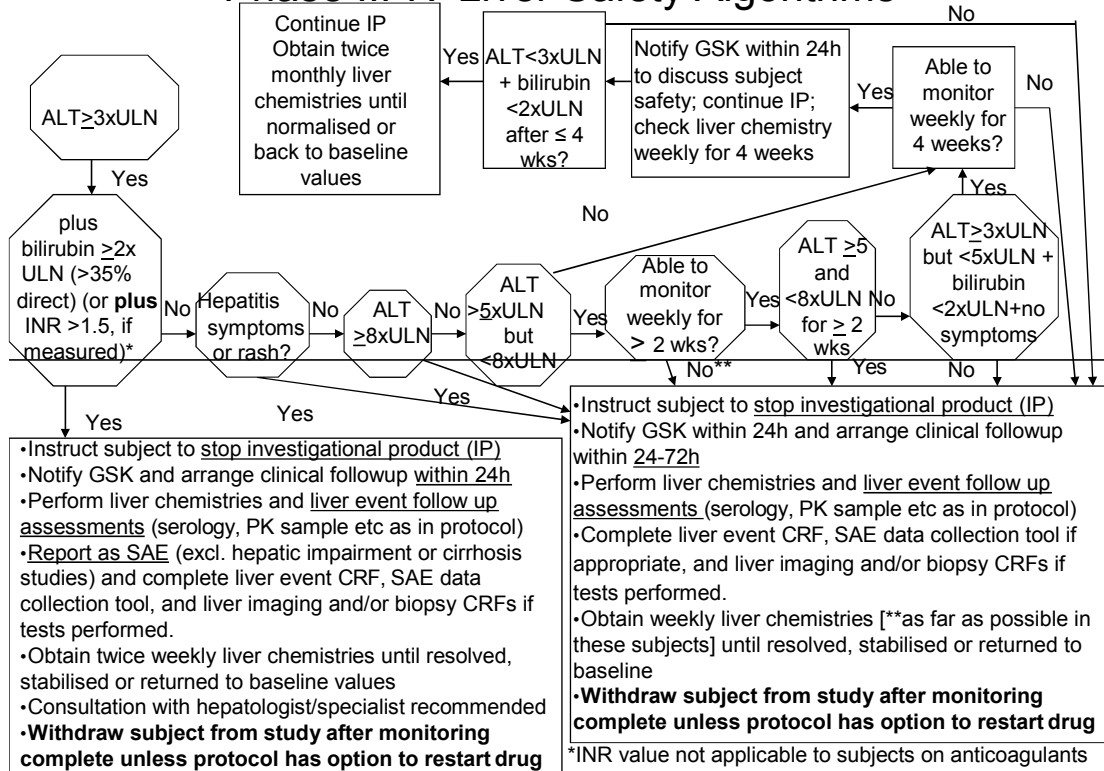
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Section 11.2., Appendix 2: Liver Chemistry Stopping and Follow-up Criteria

OLD

Phase III-IV Liver Safety Algorithms



NEW

Liver Chemistry Stopping Criteria - Liver Stopping Event	
<u>ALT-Absolute</u>	<u>ALT $\geq 8 \times \text{ULN}$</u>
<u>ALT-Increase</u>	<u>ALT $\geq 5 \times \text{ULN}$ but < 8 $\times \text{ULN}$ persists for ≥ 2 weeks</u> <u>ALT $\geq 3 \times \text{ULN}$ but < 5 $\times \text{ULN}$ persists for ≥ 4 weeks</u>
<u>Bilirubin^{1,2}</u>	<u>ALT $\geq 3 \times \text{ULN}$ and bilirubin $\geq 2 \times \text{ULN}$ (>35% direct bilirubin)</u>
<u>INR²</u>	<u>ALT $\geq 3 \times \text{ULN}$ and INR > 1.5, if INR measured</u>
<u>Cannot Monitor</u>	<u>ALT $\geq 5 \times \text{ULN}$ but < 8 $\times \text{ULN}$ and cannot be monitored weekly for ≥ 2 weeks</u> <u>ALT $\geq 3 \times \text{ULN}$ but < 5 $\times \text{ULN}$ and cannot be monitored weekly for ≥ 4 weeks</u>
<u>Symptomatic³</u>	<u>ALT $\geq 3 \times \text{ULN}$ associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</u>
Required Actions and Follow-up Assessments Following ANY Liver Stopping Event	

<u>Actions</u>	<u>Follow-up Assessments</u>
<ul style="list-style-type: none"> • <u>Immediately discontinue study treatment</u> • <u>Report the event to GSK/PPD within 24 hours</u> • <u>Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE²</u> • <u>Perform liver event follow-up assessments</u> • <u>Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)</u> • <u>Do not restart/rechallenge subject with study treatment but continue subject in the study for any protocol-specified follow-up assessments</u> <p><u>MONITORING:</u></p> <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> • <u>Repeat liver chemistries (include ALT, AST, ALP, bilirubin) and perform liver event follow-up assessments within 24 hours</u> • <u>Monitor subjects twice weekly until liver chemistries resolve, stabilize, or return to within baseline</u> • <u>A specialist or hepatology consultation is recommended</u> <p><u>For all other criteria:</u></p> <ul style="list-style-type: none"> • <u>Repeat liver chemistries (include ALT,</u> 	<ul style="list-style-type: none"> • <u>Viral hepatitis serology⁴</u> • <u>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 antibody⁵</u> • <u>A blood sample for pharmacokinetic analysis will be obtained within 12 hours of last dose (completion or discontinuation)⁶</u> • <u>Serum creatine phosphokinase and lactate dehydrogenase</u> • <u>Fractionated bilirubin, if total bilirubin $\geq 2 \times \text{ULN}$</u> • <u>Obtain complete blood count with differential to assess eosinophilia</u> • <u>Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form</u> • <u>Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over-the-counter medications.</u> • <u>Record alcohol use on the liver event alcohol intake case report form</u> <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> • <u>Antinuclear antibody, antismooth muscle antibody, type 1 antiliver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).</u> • <u>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]).</u> • <u>Liver imaging (ultrasound, magnetic</u>

<u>AST, ALP, bilirubin) and perform liver event follow-up assessments within 24 to 72 hours</u> <ul style="list-style-type: none"> • <u>Monitor subjects weekly until liver chemistries resolve, stabilize, or return to within baseline</u> 	<u>resonance, or computed tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.</u>
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AE = adverse event; 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 $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ 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 $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN (>35% direct bilirubin) or ALT $\geq 3 \times$ 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 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

<u>Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event</u>	
<u>Criteria</u>	<u>Actions</u>
<u>ALT $\geq 5 \times$ ULN and $< 8 \times$ ULN and bilirubin $< 2 \times$ ULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks.</u> <u>OR</u> <u>ALT $\geq 3 \times$ ULN and $< 5 \times$ ULN and bilirubin $< 2 \times$ ULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be</u>	<ul style="list-style-type: none"> • <u>Notify the PPD medical monitor within 24 hours of learning of the abnormality to discuss subject safety.</u> • <u>Subject can continue study treatment</u> • <u>Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize, or return to within Baseline</u> • <u>If at any time subject meets the liver chemistry</u>

<u>monitored weekly for 4 weeks.</u>	<p><u>stopping criteria, proceed as described above</u></p> <ul style="list-style-type: none"> • <u>If ALT decreases from ALT $\geq 5 \times$ ULN and $< 8 \times$ ULN to $\geq 3 \times$ ULN but $< 5 \times$ ULN, continue to monitor liver chemistries weekly.</u> • <u>If, after 4 weeks of monitoring, ALT $< 3 \times$ ULN and bilirubin $< 2 \times$ ULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.</u>
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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.

Section 11.3., Appendix 3: Cytochrome P450 3A4 Enzyme Inhibitors and Inducers

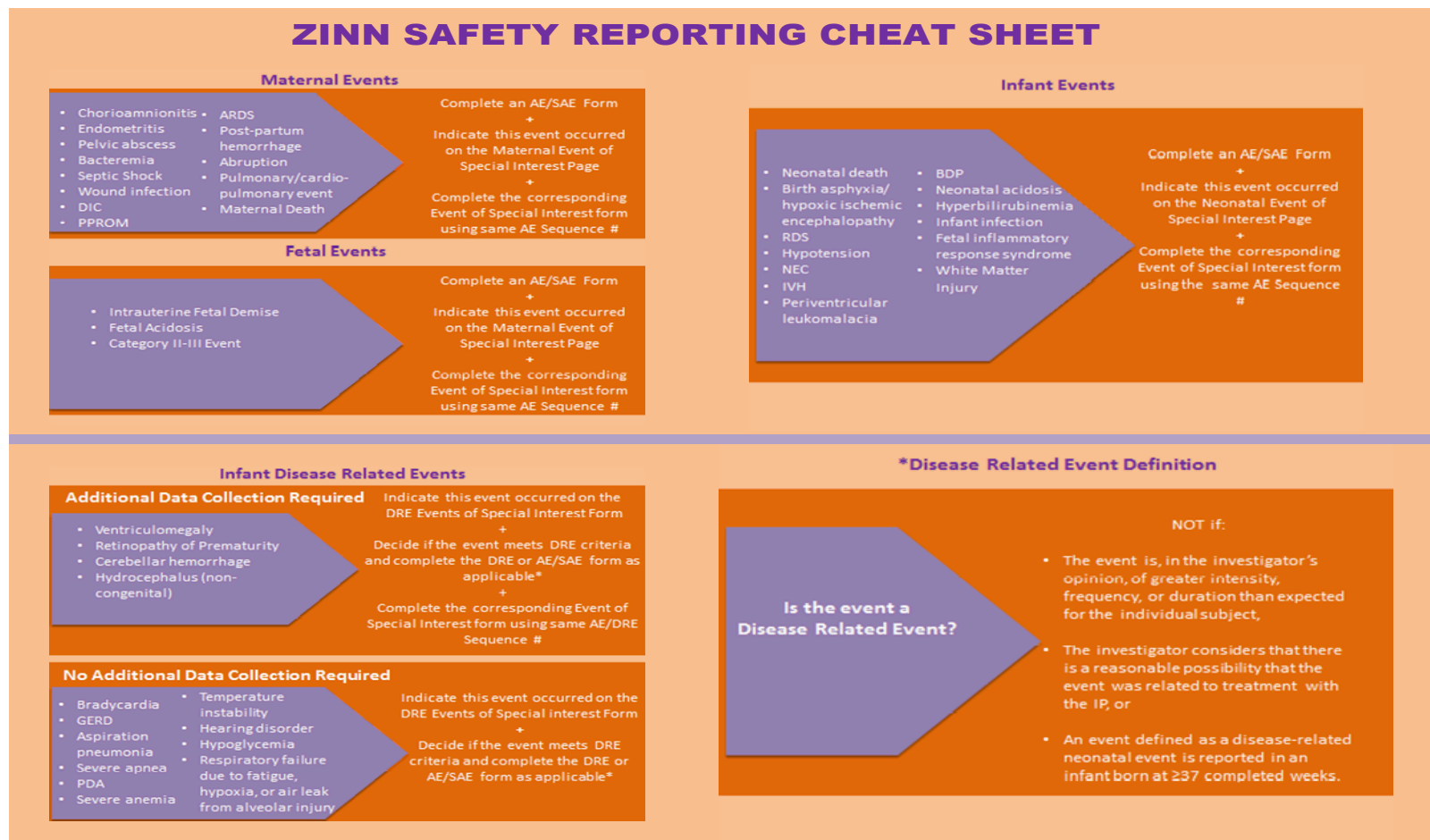
Medications that are considered cytochrome P450 3A4 enzyme (CYP3A4) inducers and inhibitors are permitted; however, concomitant administration of strong CYP3A4 inducers or strong inhibitors with the investigational product requires an adjustment to the retosiban dosing regimen (see Protocol Section 5.1 and Section 5.1.1.1).

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.

<u>Strong¹</u> <u>(Requires Adjustment to Dosing Regimen)</u>	<u>Moderate²</u>	<u>Weak³</u>
<u>Inhibitors</u>		
<u>Amprenavir</u>	<u>Aprepitant</u>	<u>Amlodipine</u>
<u>Atazanavir</u>	<u>Cimetidine</u>	<u>Atomoxetine</u>
<u>Clarithromycin</u>	<u>Darunavir</u>	<u>Atorvastatin</u>
<u>Conivaptan</u>	<u>Diltiazem</u>	<u>Azithromycin</u>
<u>Fosamprenavir</u>	<u>Erythromycin</u>	<u>Bicalutamide</u>
<u>Grapefruit juice⁴</u>	<u>Fluconazole</u>	<u>Chlorzoxazone</u>
<u>Indinavir</u>	<u>Imatinib</u>	<u>Cilostazol</u>
<u>Itraconazole</u>	<u>Nifedipine</u>	<u>Cyclosporine</u>
<u>Ketoconazole</u>	<u>Tofisopam</u>	<u>Darifenacin</u>
<u>Nefazodone</u>	<u>Verapamil</u>	<u>Dasatinib</u>
<u>Nelfinavir</u>		<u>Ezetimibe</u>
<u>Ritonavir</u>		<u>Fentanyl</u>
<u>Saquinavir</u>		<u>Fluvoxamine</u>
<u>Telithromycin</u>		<u>Gemfibrozil</u>
<u>Troleandomycin</u>		<u>Isoniazid</u>
<u>Voriconazole</u>		<u>Lacidipine</u>
		<u>Omeprazole</u>
		<u>Posaconazole</u>
		<u>Propiverine</u>
		<u>Propofol</u>
		<u>Quinidine</u>
		<u>Ranitidine</u>

<u>Strong¹</u> <u>(Requires Adjustment to</u> <u>Dosing Regimen)</u>	<u>Moderate²</u>	<u>Weak³</u>
		<u>Ranolazine</u>
		<u>Roxithromycin</u>
		<u>Tabimorelin</u>
<u>Inducers</u>		
<u>Strong¹ (Requires</u> <u>Adjustment to Dosing</u> <u>Regimen)</u>	<u>Moderate²</u>	<u>Weak³</u>
<u>Carbamazepine</u>	<u>Bosentan</u>	<u>Aprepitant</u>
<u>Efavirenz</u>	<u>Etravirine</u>	<u>Amprenavir</u>
<u>Phenytoin</u>	<u>Nafcillin</u>	<u>Avasimibe</u>
<u>Rifampin</u>	<u>Nevirapine</u>	<u>Dexamethasone</u>
<u>St. Johns Wort</u>	<u>Phenobarbital</u>	<u>Glycyrrhizin</u>
		<u>Modafinil</u>
		<u>Oxcarbazepine</u>
		<u>Pioglitazone</u>
		<u>Prednisone</u>
		<u>Rifabutin</u>
		<u>Rufinamide</u>

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 the investigational product with a strong inhibitor or strong inducer requires an adjustment to the retosiban 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 11.4., Appendix 4: 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; PPROM = preterm premature rupture of membranes; RDS = respiratory distress syndrome; SAE = serious adverse event.

11.5. Appendix 5: Summary of Human Biological Samples

Appendix 5 categorizes human biological samples as 1) those for which the results are directly related to the conduct and analysis of the study and 2) those collected and stored for future exploratory analyses. Human biological samples directly related to the study conduct and analysis include those for eligibility determination and safety, pharmacokinetics, and placental pathology. Human biological samples collected and stored for biomarker and genetic testing are categorized under future exploratory analyses. Appendix 5 also provides information regarding labeling and subject anonymization. Shipping location information for each sample is provided in the Study Procedures Manual.

The investigator should refer to the laboratory manual for complete information on sample collection and preparation, packaging and labeling, and shipping.

Human Biological Samples Directly Related to the Conduct and Analysis of the Study:

- Hematology and Chemistry: Maternal blood samples for hematology and chemistry, including liver function studies, will be collected during Screening, Day 2 of dosing, at the optional retreatment visit (if applicable), and the face-to-face post-infusion assessment visit. Labels will be customized for each test and include the protocol number, subject identification number, visit description, and date and time of collection.
- Liver Function: A maternal blood sample for liver function studies will be collected during Screening and sent to the hospital laboratory for analysis. Normal results are required to initiate dosing or continue dosing if dosing has begun before results are available. In the event liver function test results from either the local or central laboratory reveal abnormalities consistent with the liver chemistry stopping criteria defined in Protocol Section 6.3.1 and Appendix 2, additional samples will be analyzed for hepatitis A immunoglobulin M (IgM) antibody, hepatitis B surface antigen, hepatitis B core antibody (IgM), cytomegalovirus (CMV) IgM antibody, hepatitis C RNA, hepatitis E IgM antibody, Epstein-Barr viral (EBV) capsid antigen IgM antibody, creatine phosphokinase, lactate dehydrogenase, and complete blood count with differential.

If liver function test results reveal alanine aminotransferase (ALT) $>3 \times$ the upper limit of normal (ULN) AND bilirubin $>2 \times$ ULN ($>35\%$ direct bilirubin; an isolated bilirubin $>1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35) samples will also be analyzed for the following:

- Antinuclear antibody, antismooth muscle antibody, type 1 antiliver kidney microsomal antibodies, and total immunoglobulin G (IgG)
- If chronic hepatitis B is identified at study entry by a positive hepatitis B surface antigen, blood samples will be assayed for hepatitis B DNA and hepatitis delta antibody.

- Serum acetaminophen in subjects with definite or likely acetaminophen use in the preceding week.

Labels will be customized for each test and include the protocol number, subject identification number, descriptor as initial liver event assessment or follow-up, and date and time of collection.

- Urine Drug Screen: A urine sample will be collected during Screening in order to assay for ethanol and other substances of abuse for eligibility determination. The urine drug screen will be performed locally using a point-of-care, qualitative testing device.

- Pharmacokinetic Samples:

1. Maternal blood samples for quantification of retosiban plasma concentrations will be collected 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 54 hours after initiation of the infusion.
2. An umbilical cord blood sample for quantification of retosiban plasma concentrations will be collected in subjects who deliver at the investigational center within 12 hours of investigation product (IP) completion or discontinuation. Additionally, a maternal blood sample should be collected at the same time as the cord blood sample (see Section 6.5.2) if the sample time does not already coincide with one of the PK sampling windows listed above.
3. A breast milk/colostrum sample for a semi-quantitative retosiban assay will be collected in subjects who deliver at the investigational center within 12 hours of IP completion or discontinuation and are expressing breast milk/colostrum.
4. Maternal blood sample for quantification of retosiban plasma concentration within 12 hours of exposure in subjects who meet liver chemistry stopping criteria defined in Protocol Section 6.3.1.

Labels will be customized for each test and include the protocol number, subject identification number, visit description, and date and time of collection.

- Placental Pathology: A placental tissue sample will be collected for pathologic examination when delivery occurs at an investigational center. Gross examination of the intact placenta, umbilical cord, and membranes will be performed by the hospital pathology department with gross findings reported in a standardized manner. The hospital pathology department will also prepare tissue samples for histologic examination of placenta, membranes, and umbilical cord. Labels will be customized and include the protocol number, subject identification number, visit description, and date and time of collection

Human Biological Samples for Optional Future Biomarker and Genetic Testing:

Biomarker and genetic testing will be performed in relation to the study treatment and preterm labor condition.

- Biomarker Samples:

1. Maternal blood samples for biomarker analysis will be collected for all subjects

during Screening.

2. **An umbilical cord blood sample for biomarker analysis will be collected in subjects who deliver at the investigational center.**

Labels will be customized for each test and include the protocol number, subject identification number, visit description, and date and time of collection.

- **Genetic Samples:**
 1. **Maternal blood samples for genetic analysis will be collected during Screening for subjects who consent to participate. Refer to Appendix 1 for a description of genetic testing objectives, assessments and procedures, subject participation, and confidentiality of data. Labels will be customized for each test and include the protocol number, subject identification number, visit description, and date and time of collection.**
 2. **An umbilical cord blood sample for genetic analysis will be collected in subjects who deliver at the investigational center. Labels will be customized for each test and include the protocol number, subject identification number, visit description, and date and time of collection.**

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 the 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.
- Clarify that an abdominal ultrasound to assess fetal growth is needed at Screening or before retreatment unless the most recent ultrasound is within 3 weeks (21 days) before the date of randomization or the date of retreatment. 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 or retreatment.

- Updated the list of maternal drug-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.
- Removed changes detailed in the country-specific amendment for sites in France because subjects in this country will not be recruited for this study.
- 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

Sponsor Information Page

Sponsor Medical Monitor Contact Information and Sponsor Serious Adverse Events (SAE) Contact Information:

Issue	Latin America Contact	Europe/Asia Contact
Safety Questions	PPD [REDACTED] MD Medical Director, Medical Affairs and Pharmacovigilance PPD Buenos Aires, Brazil	Europe: PPD [REDACTED] MD, MFPM Associate Medical Director, Medical Affairs and Pharmacovigilance PPD Sofia, Bulgaria Warsaw, Poland Asia: PPD [REDACTED] MD Associate Medical Director, Medical Affairs and Pharmacovigilance PPD Kuala Lumpur, Malaysia
	24-Hour Safety Hotline: PPD [REDACTED] Safety Fax: PPD [REDACTED]	Safety Hotline: PPD [REDACTED] Safety Fax: PPD [REDACTED]
SAE Reporting	24-Hour SAE Hotline: PPD [REDACTED] SAE Fax: PPD [REDACTED]	

List of Abbreviations

PCP—phenylelidine

Protocol Summary, Study Design

For undelivered subjects who are subsequently diagnosed with recurrent preterm labor following the Inpatient Randomized Treatment Phase, retreatment with blinded investigational product (IP) is permitted. Retreatment is limited to a single repeat course

of the blinded IP to which the subject was originally randomly assigned, either retosiban or atosiban. Retreatment is only permitted if the subject presents prior to 33^{6/7} weeks' gestation and meets all the eligibility criteria **specified in the Time and Events Table**.

The subject or other legal guardian for the infant will also be asked to consent to participate in a separate 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 face-to-face post-infusion assessment visit. ~~(Note: In France, consent for the infant study is required during the Screening Phase, see Section 4.2 [inclusion criterion 1] and Section 3.1.1).~~

An interim analysis will occur after **approximately** 130 subjects have completed delivery and have time to-delivery results available. At the interim analysis, all available safety and efficacy data will be reviewed by an unblinded independent data monitoring committee who may make recommendations to terminate the study.

Section 3.1., Study Design

The subject or other legal guardian for the infant will also be asked to consent to participate in a separate 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 face-to-face post-infusion assessment visit. ~~(Note: In France, consent for the infant study is required during the Screening Phase, see Section 4.2 [inclusion criterion 1] and Section 3.1.1).~~

An interim analysis will occur after **approximately** 130 subjects have completed delivery and have time to-delivery results available. At the interim analysis, all available safety and efficacy data will be reviewed by an unblinded independent data monitoring committee (IDMC) who may make recommendations to terminate the study (see Section 9.8). Details of the interim analysis are provided in Section 8.3.4. Subjects will continue to be enrolled while the interim analysis is being conducted.

Randomized treatment can be discontinued as outlined in Section 4.4.2. Subjects discontinuing randomized treatment will be managed according to the standard care and asked to remain on study through the Maternal Post Delivery Assessment Phase. These subjects will also be asked to consent to the infant follow-up study, ~~with the exception of subjects in France (see Section 4.2 and Section 3.1.1).~~

Section 3.1.1., Screening Phase

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 sign measurements, cervical examination, medical and obstetric history, estimated GA). However, 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 the consent having been signed. ~~Additionally, in France, subjects providing consent to participate in ZINNa Screening must also provide signed and dated written consent for their infant to participate in the infant follow-up study (200722 [ARIOS]) (see Section 4.2).~~

Section 3.1.2.1., Before Treatment

Prior to dosing, the investigators must confirm the fetal heart rate pattern remains reassuring, ~~the uterine contraction rate is not less than 4 contractions over a 30-minute interval~~ **that, according to medical discretion, tocolytic therapy is still indicated**, and the electrocardiogram (ECG) does not have clinically significant abnormalities (see Section 6.1). ~~In addition, at the discretion of the investigator and as clinically indicated, a cervical examination may be performed to ensure that cervical dilation does not exceed - 4 cm.~~

Section 3.1.2.3., End of Treatment

The subject or other legal guardian for the infant (both delivered and undelivered) will be asked to consent to participate in a separate long-term infant follow up study for safety and neurodevelopment, if not already obtained. ~~Note: In France, consent for the infant study is required during the Screening Phase (see Section 4.2 and Section 3.1.1).~~

Section 3.1.3.1., Retreatment

For undelivered subjects who are subsequently diagnosed with recurrent preterm labor 24 hours or more following completion of the Inpatient Randomized Treatment Phase, retreatment with blinded IP is permitted at the discretion of the investigator. Retreatment is limited to a single repeat course of the blinded IP to which the subject was originally randomly assigned, either retosiban or atosiban. Retreatment is only permitted if the subject experiences a spontaneous preterm labor recurrence before 33^{6/7} weeks' gestation and meets ~~all the eligibility criteria~~ **specified in the Time and Events Table (Table 5)**. Atosiban retreatment guidelines are provided in the summary of product characteristics (SmPC) [Tractocile SmPC, 2013].

Section 3.1.5., Maternal Post-Delivery Assessment Phase

The subject or other legal guardian will be asked to provide consent for the infant (whether delivered or undelivered) to participate in a separate infant follow up study for safety and neurodevelopment, if not already obtained. ~~Note: In France, consent for the infant study is required during the Screening Phase (see Section 4.2 and Section 3.1.1).~~

Section 4.2., Inclusion Criteria

1. Signed and dated written informed consent is required prior to a subject's participation in Study 200721 (ZINN) 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.

~~**French Subjects:** Participation in Study 200721 (ZINN) also requires that the subjects provide signed and dated written consent for her infant to participate in Study 200722 (ARIOS), a follow-up study assessing long-term safety and outcomes in infants born to mothers participating in retosiban treatment studies.~~

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.

3. 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 4.3., Exclusion Criteria

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 positive findings for substances other than cocaine, PCP, methamphetamine, or amphetamine is at the investigator's discretion (examples include alcohol, cannabinoids, and opiates)~~
- 10 2. 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.~~ Women with documented active hepatitis B or hepatitis C viral infection, unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
- ~~121.~~ History of sensitivity to the IPs or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK/PPD medical monitor, contraindicates their participation.

Section 4.4.1.1., 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~~ **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 ECG cannot be dosed and should 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 4.4.2., Discontinuation of Investigational Product

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.

~~The investigator should consult the PPD medical monitor prior to discontinuing any subject from the IP based on urine drug screen results that become available after the IP has been initiated.~~

Subjects discontinuing the IP who have not yet delivered will continue in the study through delivery and the maternal post-delivery assessment. 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. ~~Note: In France, consent for the infant study is required during the Screening Phase (see Section 4.2 and Section 3.1.1).~~

Section 5.1., Investigational Product and Other Study Treatment

Atosiban (Tractocile, Ferring Pharmaceuticals) active comparator will be provided ~~by~~ **to** the site. Atosiban is a marketed product that is a clear, colorless solution for infusion that contains atosiban at 6.75 mg/0.9 mL

Section 6., Study Assessments and Procedures

Table 5, Time and Events Table

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery ³	Delivery to 28 days post EDD	
Clinical and Other Assessments										
Written informed consent and medical releases for treatment ⁴	X									
Discuss and request consent for participation in the infant follow-up study ⁵		X ⁵ X								X
Inclusion/exclusion criteria confirmation	X			X						
Subject demography	X									
Medical history (including obstetrics history) ⁶	X				X		X	X		
Urine drug screen ⁷	X			X						
Physical examination (including height and weight)	X									
Cervical examination ⁸	X	X	X	X	X					

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery ³	Delivery to 28 days post EDD	
Estimated fetal weight and head circumference via ultrasound ⁸	X			<u>X</u>						
Determine AFI via ultrasound ⁹	X			<u>X</u>						
Uterine contractions ¹⁰	X									
Schedule face-to-face post-infusion assessment visit			X							
Investigational Products¹¹										
Investigational product (retosiban or atosiban)		X	X	<u>X</u>						
Efficacy Assessments										
Date and time of delivery							X ¹²			
Mode of delivery							X ¹²			
Indication for delivery							X ¹²			
Neonatal composite outcomes									X	
Neonatal hospital stay									X	

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery ³	Delivery to 28 days post EDD	
Maternal Safety Assessments										
Concomitant medications			X					X		X
ECG 12-lead ¹³	X									
Vital sign measurements (BP, pulse rate, respiratory rate, and temperature) ¹⁴	X	X	X	X	X					
AEs, SAEs, and DREs: maternal			X					X		X
Breastfeeding status								X		
Edinburgh Postnatal Depression Scale ¹⁵ (maternal)								X		
Local laboratory assessments (LFTs only) ¹⁶	X			X						
Central laboratory assessments (including hematology, chemistry, and LFTs) ¹⁷	X		X	X	X ¹⁷					
Physical examination (brief)					X					
Status of postpartum bleeding								X		

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery ³	Delivery to 28 days post EDD	
Fetal Safety Assessments										
Electronic fetal monitoring	X ¹⁸	X ¹⁹	X ¹⁹	X ¹⁹	X ²⁰		X ²¹			
AEs/SAEs: fetal			X				X			
Neonatal Safety Assessments										
AEs, SAEs, and DREs: neonatal							X		X	
Neonatal Apgar Scores (1 and 5 minutes)							X ¹²			
Neonatal growth parameters							X ¹²			
Neonatal blood gases							X ¹²			
Health Outcome Assessments										
Maternal and neonatal health care resource use ²²							X		X	
EQ-5D-5L (maternal)		X						X ³		
Pharmacokinetic Assessments										
Maternal PK blood sample ²³		X ²³	X ²³							
Cord blood sample ²⁴							X			
Breast milk/colostrum sample ²⁵							X			
Histopathology										
Placental tissue sample ²⁶							X			

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Retreatment ¹	Post-Infusion Assessment Phase ²		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery ³	Delivery to 28 days post EDD	
Biomarker Assessments										
Genetic blood sample for maternal DNA ²⁷	X									
Blood sample for maternal inflammation biomarker	X									
Biomarker and genetic cord blood sample ²⁸							X			
Other Assessments										
Fetal fibronectin (optional) ²⁹	X			X						
Cervical length via transvaginal ultrasound (optional) ³⁰	X			X						

5. The subject or other legal guardian for the infant will be asked to consent to participate in a separate long-term study to follow infants for safety and neurodevelopment outcomes. The subject or other legal guardian for the infant (both delivered and undelivered) will be asked to give consent for the infant follow-up study at any time during the study that is appropriate and convenient. (~~Note: In France, consent for the infant study is required during the Screening Phase (see Section 4.2 and Section 3.1.1).~~ Withdrawal from the study after beginning randomized treatment or discontinuing IP does not preclude involvement in the infant follow-up study.
6. 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.
7. ~~The urine drug screen will be performed locally using a point-of-care, qualitative testing device.~~
8. 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 pre-dosing 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~~ **are not required but may** be performed based on investigator discretion. **If inclusion criteria is based on cervical change (see Section 4.2), 2 examinations must be documented (either 2 digital cervical examinations or 2 cervical length examinations).**
8. **An ultrasound for estimation of fetal weight and head circumference is needed at Screening or before retreatment unless the date of the most recent ultrasound that includes fetal weight and head circumference is within 3 weeks (21 days) before the date of randomization or retreatment.**
 9. The abdominal ultrasound for determination of the AFI will be performed at Screening **and before retreatment. The AFI should be measured using the 4-quadrant method.**
 10. Uterine tocography or manual palpation (if necessary) will be performed **at Screening** ~~prior to dosing to confirm the uterine contraction 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.~~
 14. **Vital signs (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, if criteria are met, also during retreatment**, and at the post-infusion assessment visit. During the Inpatient Randomized Treatment Phase **and during retreatment**, vital signs will be assessed and recorded within the following windows relative to the start of the infusion: 15 to 30 minutes, 4 to 8 hours, and 20 to 24 hours, at the end of the infusion, at the time of any dose changes, and as warranted by a medical condition. It is suggested (but not required) that oxygen saturation also be assessed at Screening and recorded in source documents.
 15. Maternal subjects will complete the EPDS, a self-reported questionnaire, at the maternal follow-up assessment 6 weeks (-2 weeks/+6 weeks) after delivery.
 16. 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 $\geq 2 \times \text{ULN}$ OR total bilirubin is not $> 1.5 \times \text{ULN}$ ($> 35\%$ direct bilirubin) ~~before dosing with the IP.~~ An isolated bilirubin $> 1.5 \times \text{ULN}$ 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 **or for the start of dosing with IP;** however, see Section 6.3.1 if ALT or bilirubin is abnormal.

Section 6.1., 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 4.2). 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 $\geq 2 \times \text{ULN}$ OR bilirubin is not $> 1.5 \times \text{ULN}$ ($> 35\%$ direct bilirubin), if available (see Section 6.3.1). An isolated bilirubin $> 1.5 \times \text{ULN}$ is acceptable if bilirubin is fractionated and direct bilirubin is $< 35\%$. Dosing may be started prior to the availability of these results.
- 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~~ **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 4.4.1).

Section 6.3.7., Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The DREs listed in Section 6.3.7.1 and Section 6.3.7.2 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 6.3.7.1, 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 6.3.7.2 applies**
- **Hospitalization for delivery, unless prolonged or one of the conditions listed at the end of Section 6.3.7.2 applies**

Section 6.3.7.2., Disease-Related Neonatal Events (Occurring in Infants Born Prior to 37 Completed Weeks)

Because these events (Section 6.3.7.1 and Section 6.3.7.2) 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 an SAE). These events will be recorded on the DRE page in the eCRFs. These DREs will be monitored by the IDMC and 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 using the standard process, as summarized in Section 6.3.11:

Section 6.3.12.2., Vital Sign Measurements

Vital signs (bBlood pressure, pulse rate, respiratory rate, and temperature) will be measured at the following time points during the study: Screening, Inpatient Randomized Treatment Phase, **retreatment (if criteria are met, see Section 3.1.3.1)**, and at the face to face post-infusion assessment visit. During the Inpatient Randomized Treatment Phase **and during retreatment**, vital signs 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. It is suggested (but not required) that oxygen saturation also be assessed at Screening and recorded in source documents.

Section 6.3.12.4., 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 4.3). **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 ~~4~~3 weeks of Screening, with the results and date of assessment recorded in the eCRF).

If the investigator determines a subject suitable for retreatment (see Section 3.1.3.1 for retreatment criteria), an abdominal ultrasound to assess fetal growth should be performed unless records are available documenting ultrasound-derived estimated fetal weight and head circumference within 3 weeks of retreatment, with the results and date of assessment recorded in the eCRF.

Section 6.3.12.5., Laboratory Assessments

The following laboratory tests will be performed locally:

- Liver function tests, including ALT and bilirubin, performed at Screening (see Section 6.3.1)
- ~~Urine drug screen using a point of care, qualitative testing device~~

The biological samples collected over the course of the study that are directly related to the conduct and analysis of the study, including hematology and chemistry tests, **and** liver function tests, ~~and urine drug screening~~ are summarized further in Appendix 5.

Section 11.5., Appendix 5: Summary of Human Biological Samples

Labels will be customized for each test and include the protocol number, subject identification number, descriptor as initial liver event assessment or follow-up, and date and time of collection.

- ~~**Urine Drug Screen:** A urine sample will be collected during Screening in order to assay for ethanol and other substances of abuse for eligibility determination. The urine drug screen will be performed locally using a point of care, qualitative testing device.~~