Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan

Title	:	Randomized, Double-Blind, Multicentre, Phase III Study Comparing the Efficacy and Safety of Retosiban Versus Placebo for Women in Spontaneous Preterm Labor
Compound Number	:	GSK221149
Effective Date	:	08-SEP-2017

Description:

- The purpose of this reporting and analysis plan (RAP) is to describe the final planned analyses and output to be included in the Clinical Study Report for Protocol 200719.
- This RAP is intended to describe the planned efficacy (primary, secondary and exploratory) and safety analyses required for the study.
- This document will be provided to the study team members to convey the content of the final Statistical Analysis Complete (SAC) Deliverable.

Author's Name and Functional Area:

PPD Manager, Biostatistics, PPD	08-SEP-2017
PPD Biostatistician, PPD	08-SEP-2017

Approved by:

PPD Manager Statistics, GlaxoSmithKline	08-SEP-2017
Signature: PPD	08-SEP-2017

TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This Reporting and Analysis Plan (RAP) details all planned efficacy and safety analyses and outputs required for the final Clinical Study Report (CSR) of study 200719.
Protocol	• This RAP is based on the original protocol (Dated: 26-Nov-2014), original protocol republished to make Section 6.4 (Blinding) consistent with the protocol template(Dated: 17-Feb-2015), protocol amendment 01(Dated: Aug-13-2015), protocol amendment 02 (Dated 14-Sep-2015), country-specific amendment 03 (Italy; Dated: 19-Apr-2016) and protocol amendment 04 (Dated: 20-Jun-2016) for study GSK200719 [GlaxoSmithKline Document Numbers: 2014N194467_00, 2014N194467_01, 2014N194467_02, 2014N194467_03, 2014N194467_04 and 2014N194467_05
Primary Objective	• To test the null hypothesis in the ITT Population that there is no difference between retosiban and placebo versus the alternative hypothesis that there is a difference between the 2 co-primary endpoints.
Primary Endpoint	• Time to delivery or treatment failure, whichever occurs first • Proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite determined up to 28 days after the estimated date of delivery (EDD) of 40 0/7 weeks
Study Design	• Phase III, randomized, double-blind, double-dummy, placebo-controlled, parallell-group, multicenter study to investigate efficacy and safety of 6-mg IV loading dose of retosiban over 5 minutes, followed by a 6-mg/hour continuous infusion over 48 hours in women aged 18 to 45 years (Sweden) or aged 12 to 45 years (all other countries) with an uncomplicated singleton pregnancy in preterm labor with intact membranes between $24^{0/7}$ and $33^{6/7}$ weeks' gestation. • The study was terminated due to fesibility reason. The study enrolled 25 patients and patients were randomly assigned to one active arm (retosiban) and one control arm(placabo).
Planned Analyses	• Interim analyses are described in Independent Data Monitoring Committee (IDMC) RAP. • Final efficacy and safety analyses are detailed within Section 3.2. • All decisions regarding final analyses, as defined in this RAP document, will be made prior to Database Freeze (unblinding) of the study data.
Primary Analysis Population	• The Maternal and Neonatal Safety Analysis Population will be used to evaluate safety. • The Intent-to-treat (ITT) Maternal and Neonatal Analysis Populations will be used to evaluate efficacy.
Hypothesis	• Due to the early termination of this study, no formal statistical analysis will be performed for the time to delivery or treatment failure endpoints.
Primary Analyses	• Due to the early termination of this study, no formal statistical analysis will be performed for the co-primary endpoints. But, summary statistics by treatment group will be provided.

Secondary Analyses	• Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. • Due to the early termination of this study, no formal statistical analysis will be performed for the secondary endpoints. But, summary statistics by treatment group will be provided.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

This study was terminated due to feasibility. Due to the low number of subjects involved, the analysis is modified and certain analysis won't be performed. Please refer to below section for more details.

2.2. Study Objective(s) and Endpoint(s)

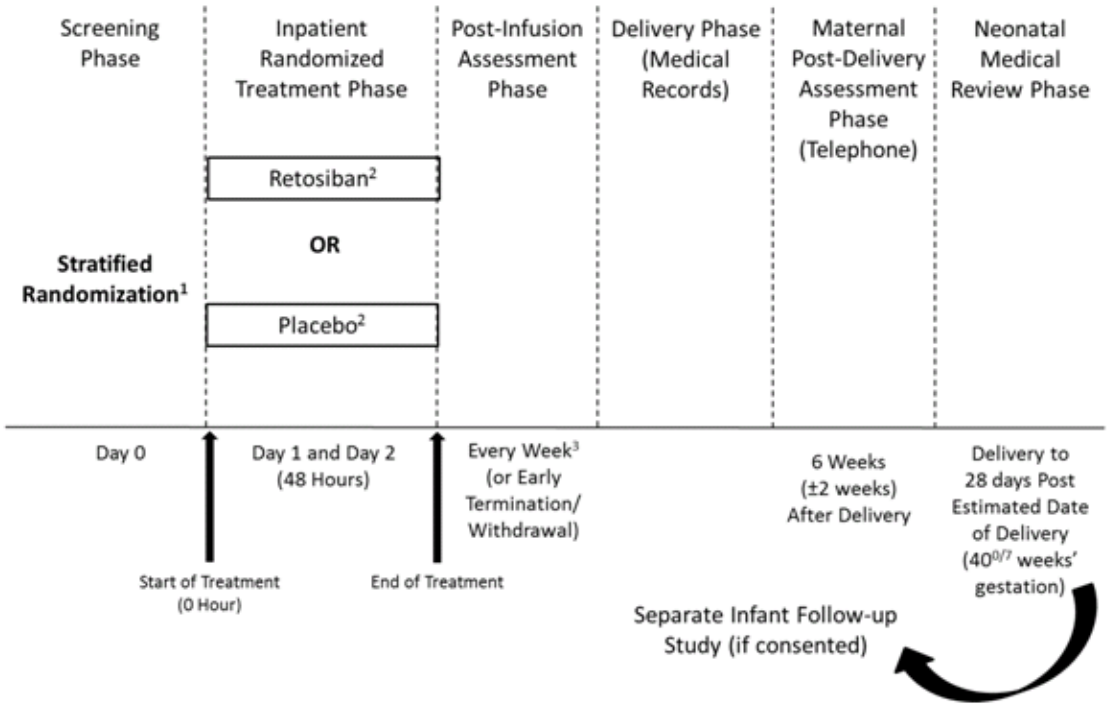
Objectives	Endpoints
Primary	**Primary**
• To demonstrate the superiority of retosiban to prolong pregnancy compared with placebo.	• Time to delivery or treatment failure, whichever occurs first. Time to delivery will be calculated from the start of study treatment administration until delivery. Time to treatment failure will be calculated from the start of study treatment administration to the administration of any putative tocolytic medication • Proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite determined up to 28 days after the estimated date of delivery (EDD) of $40^{0/7}$ weeks
	Supportive Key Secondary
	• Time to delivery • 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
	Supportive Other Secondary
	• Proportion of neonates with each individual component of the composite neonatal morbidity and mortality • Neonatal admission to a specialized care unit and length of stay – confirm admission to neonatal intensive or

Objectives	Endpoints
	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 • Proportion of births prior to $28^{0/7}$ weeks' gestation • Proportion of births prior to $32^{0/7}$ weeks' gestation • Proportion of births prior to $35^{0/7}$ weeks' gestation • Proportion of births ≤7 days from the first study treatment • Proportion of births ≤48 hours from the first study treatment • Proportion of births ≤24 hours from the first study treatment
Secondary	**Secondary**
• To describe the maternal, fetal, and neonatal safety profile during and after IV retosiban treatment compared with placebo	<u>Endpoints for Mother</u> • Incidence of maternal Adverse Events (AEs) and Serious Adverse Events (SAEs) • Significant changes in maternal vital signs and maternal 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 disease-related events <u>Endpoints for Fetus</u> • Incidence of fetal AEs and SAEs • Fetal acidosis • Fetal AEs of special interest <u>Endpoints for Neonate</u> • Neonatal APGAR scores, growth parameters at birth and at discharge • Incidence of neonatal AEs and SAEs • Neonatal AEs of special interest • Neonatal disease-related events
• To determine the effect of retosiban treatment compared with placebo on health care resource use for the maternal and neonatal hospitalizations	• 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)

Objectives	Endpoints
• 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	• Population PK analysis is not performed.

2.3. Study Design

Overview of Study Design and Key Features



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

Overview of Key Study Design Features	
Design Features:	• Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study • Subjects are females, aged 12 to 45 years (all other countries including UK, Japan and US), with an uncomplicated, singleton pregnancy and intact membranes in preterm labor between $24^{0/7}$ and $33^{6/7}$ weeks of gestation.
Dosing:	• 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. • Normal saline 0.9% NaCl administered intravenously will serve as the placebo control. The normal saline infusion will be matched for the retosiban volume, IV loading dose over 5 minutes, and continuous infusion rate, including a dose increase in subjects with an inadequate response any time after the first hour of treatment.
Treatment Assignment:	• A total of 25 patients were blindly randomly assigned to retosiban or placebo in a 1:1 ratio. • Subjects were stratified by established progesterone treatment (Yes/No) and gestational age at randomization ($24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$ and $31^{0/7}$ to $33^{6/7}$. • Subjects within each stratum were randomly assigned in 1:1 ratio to receive either retosiban or placebo using an IVRS in accordance with the randomization schedule.
Interim Analysis	• There was no interim analysis being conducted since there study was terminated before inteirm analysis.

2.4. Statistical Hypotheses

The co-primary endpoints assess prolongation of pregnancy using time to delivery or treatment failure, whichever comes first, and neonatal outcomes using a morbidity and mortality composite.

Due to the early termination of this study, no formal statistical analysis will be performed for the time to delivery or treatment failure endpoints. But summary statistics will be provided.

3. PLANNED ANALYSES

All planned analyses will be done using SAS version 9.3 or higher. The Analysis Data Model (ADaM) will be created per ADaM implementation guide version 1.1. Details on derivation of variables will be specified in the specification document of ADaM. All analysis tables, listings and figures will be generated based on ADaM and/or Study Data Tabulation Model (SDTM).

3.1. Interim Analyses

No interim analysis was conducted.

3.2. Final Analyses

The final planned analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and the final database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the study have been met.
4. Randomization codes have been distributed.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Randomized	• Consists of all mothers randomly assigned to treatment regardless of whether they actually are treated. • Subjects will be presented by their planned randomized treatment	• Subject Disposition
Randomized but not dosed	• Consists of all mothers that are randomized but fail to receive any study treatment. • Subjects will be presented by their planned randomized treatment.	• Subject Disposition
Maternal Safety	• Mothers randomly assigned to treatment who 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. Any subject who received both treatments (retosiban and placebo) will be assigned to retosiban group for actual treatment.	• Maternal and fetal safety
Neonatal Safety	• Consists of neonates whose mothers received randomized treatment. • Subjects are analyzed according to the actual treatment their mothers received. • Any subject who received both treatments (retosiban and placebo) will be assigned to retosiban group for actual treatment.	• Neonatal safety
Maternal ITT	• Consists of all mothers randomly assigned to treatment 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 will be presented separately.	• Maternal and fetal efficacy endpoints
Neonatal ITT	• Dataset comprises all neonates whose mothers are the randomized Subjects who have been exposed to study drug, i.e., mothers from the ITT Population.	• Neonatal efficacy endpoints

NOTE :

- Please refer to Section 11.11 Appendix 11: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Significant protocol deviations (including deviations related to study inclusion/exclusion criteria, study treatment, conduct of the trial, patient management or patient assessment) will be listed.
- Protocol deviations are tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (Reference).
    - Data will be reviewed prior to unblinding and freezing the database to ensure all significant protocol deviations and non-significant deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Subgroups

There will be no subgroup analysis due to limited number of subjects enrolled because of early termination of the study.

5.2. Multiplicity Adjustment

There will be no multiplicity adjustment due to early termination of the study.

No formal tests of hypothesis will be performed on safety data.

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
11.1	Appendix 1: Protocol Deviation Definitions
11.2	Appendix 2: Time and Events
11.3	Appendix 3: Treatment States and Phases
11.4	Appendix 4: Data Display Standards & Handling Conventions
11.5	Appendix 5: Derived and Transformed Data
11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
11.7	Appendix 7: Primary and Sensitivity Analyses for Co-Primary Endpoints with Missing Data
11.8	Appendix 8: Values of Potential Clinical Importance
11.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
11.10	Appendix 10: Abbreviations & Trade Marks
11.11	Appendix 11: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Planned Analyses Overview

The study population analyses will be based on the population specified in Section 0.

Table 2 provides an overview of the planned study population analyses with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated		
	Table	Figure	Listing
Randomization			
Randomization			Y
Subject Disposition			
Study Populations [1]	Y		Y
Subject Disposition [1]	Y		Y
Reasons for Withdrawals [2]	Y		Y
Significant Protocol Deviations [2]	Y		Y
Subjects by Site [3]	Y		Y
Demography			
Demographics and Baseline Characteristics [2]	Y		Y
Race & Racial Combinations [2]	Y		Y
Medical Condition & Concomitant Medications			
Medical History/Conditions (Obstetrical/Prenatal) [2]	Y		Y
Prior/Concomitant Medication [3]			Y
Obstetrical Medication, Magnesium Sulfate and Antenatal Corticosteroids [3]	Y		Y

NOTES:
1. Displays generated using the all randomized subjects.
2. Displays generated using the ITT population.
3. Displays generated using the Safety population.

6.2. Disposition of Subjects

Subject status with respect to the infusion of the investigational product (IP) will be summarized in relation to:

- Randomized and not dosed
- Study completion and withdrawal

- IP Discontinuation

- Dose increase

- The number and percentage of subjects who complete or withdraw from the study will be summarized by treatment group. Reasons for withdrawal from the study will also be summarized.

The number and percentage of subjects with the above IP status will be reported by treatment group. Reasons for IP discontinuation will be presented. Also, the number and percentage of subjects who are randomized to IP but not dosed will be reported by treatment group.

A completed subject is defined as one who has completed all phases of the study including the post-delivery assessment and neonatal medical review phase. 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. Also, the number and percentage of subjects withdrawn prior to IP completion and after IP completion will be reported.

Subject disposition data will also be listed. All disposition summaries will be performed using all randomized subjects.

6.3. Demographic and Baseline Characteristics

For mothers, continuous variables, such as age (years), weight (kg), height (cm), BMI (kg/m^2), gestational age at randomization (weeks/day), contraction frequency, cervical dilation (cm), cervical length (mm), fFN (continuous) and other baseline characteristics as needed will be summarized using descriptive statistics by treatment group. Since only year of birth is collected and the month and day of birth are not collected, a mother's age will be calculated using below algorithm.

- The day and month is imputed as '30th June'.
- The age of mother is calculated as the difference of the date of the first study treatment and the date of birth divided by 365.25. For example, if the date of the randomization was at 00:00 am on 20 March 2015 and date of birth was 1987, the age is 27.
- If no inclusion deviation in age requirement, the age is between 12 and 45 year old based on study entry criteria.
- The mother is recorded as an adolescent in CRF if she is adolescent (12 to < 18 years of age), so age will be adjusted. For example, the calculated age is 18.2 but a subject is marked as an adolescent in CRF, a subject's age is to 18.

GA at randomization in weeks/days will be obtained from CRF and will be converted into numeric value as covariate in the statistical analysis of primary and secondary endpoint. Please refer to Appendix 11.6.2 for missing GA at randomization.

The following categorical variables will be summarized by reporting the number and percentage of subjects in each category by treatment group:

- Race
- Ethnicity
- GA at randomization (4 strata)
- Established progesterone use
- Country
- Prior tocolytic use in current episode (Beta-mimetics, Magnesium Sulfate, Calcium channel Blockers, NSAIDs, and Oxytocin receptor antagonists)
- Adolescent (between 12-<18 years) and adult (>= 18 years) patients.
- fFN (positive or negative)

For fetus, continuous variables, such as estimated weight (g) and AFI results (cm) measured using the 4-quadrant method will be summarized.

Demographic and baseline characteristics data will also be listed. Summaries will be performed using ITT population. For mothers/fetus, demographic and baseline characteristics will be presented in a separate table. Additional baseline characteristics which are not listed above can be included in the final analysis.

Races and racial combinations will be presented in a separate table following GSK race reporting standards.

6.4. Medical Conditions (Current/Past)

The number and percentages of subjects with obstetrical history, and prenatal history will be presented.

In addition, subject level listings of, obstetrical history and prenatal history will be listed.

All summaries will be performed using the Maternal ITT Population.

6.5. Concomitant Medication

Any prior and concomitant medication used during the study will be recorded and coded using World Health Organization Drug Dictionary (WHODRUG), which will be updated whenever available throughout the life of the study. Summary of all medications by treatment group and preferred term will be provided in relation to treatment phase (prior medication or concomitant medication). Prior medications are those started before the first study treatment. Concomitant medications are those taken at any time on or after the day of the first treatment during the study period, including those medications that were started prior to randomization but were continued into the study period. If the medication are taken prior to start of IP and continue into the study period, the medication will be included as both prior and concomitant medication.

For mothers, all prior and concomitant medications will be listed using verbatim and preferred terms. All summaries will be performed using the Maternal Safety Population.

In addition, obstetrical medication, magnesium sulphate, and antenatal corticosteroids used during the study will be summarized and listed separately for the Maternal Safety Population.

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

There is no hypothesis testing for the co-primary endpoints - time to delivery or treatment failure and neonatal composite outcome. The co-primary endpoint will be summarised and listed by treatment in the ITT Population.

Table 3 provides an overview of the planned efficacy analyses with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 3 Overview of Planned Efficacy Analyses

	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Time to delivery or treatment failure [1]				Y			Y
Neonatal composite endpoint [1]				Y			Y
Individual neonatal composite endpoint[1]t				Y			Y
Neonatal composite endpoint without RDS [1]				Y			Y
Neonatal composite endpoint without RDS and mortality [1]				Y			Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Displays generated using the 'ITT' population.

Following review of the data, additional analyses may be conducted to further support the evaluation and interpretation of the data.

7.1.2. Planned Statistical Analyses

The time to delivery is calculated as the days between the delivery and start time of the infusion of IP using the formula below:

Time to delivery (days) = date/time of delivery – date/time of start of infusion

The exact date/time of delivery and infusion will be used to determine the time to delivery.

Time to delivery is a continuous numeric value with one decimal place (e.g. expressed as xx.x days) and the exact date/time of delivery and infusion will be used to determine the time to delivery. For example, if the date/time of delivery was at 00:00 am on 20 March 2015 and date/time of start of infusion was at 12:00 pm on 01 March 2015 APR2015, time to delivery is 19.5 (days).

Treatment failure will be defined as the administration of any putative tocolytic medication for active preterm labor or as prevention of preterm labor, such as calcium-channel blockers, NSAIDs, or β-agonists, apart from the exceptions listed in Protocol Section 6.12.1.2.1 **Error! Reference source not found.**, and magnesium sulfate doses that exceed a 4- to 6-g IV loading dose and 1- to 2-g/hour infusion rate and total duration of magnesium sulfate administration greater than 48 hours (see Protocol Section **Error! Reference source not found.**). The time to treatment failure will be assessed from the start of study treatment administration (time 0) in the Inpatient Randomized Treatment Phase until a putative tocolytic is administered.

Times to deliver or treatment failure is defined as time to delivery or time to treatment failure whichever occurs first.

No formal statistical analysis will be performed but summary statistics will be provided.

8. SECONDARY AND EXPLORATORY ANALYSES

8.1. Secondary Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the Maternal and Neonatal ITT Populations.

Table 4 provides an overview of the planned efficacy analyses with further details of data displays presented in Appendix 11: List of Data Displays.

Table 4 Overview of Planned Efficacy Analyses

	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Supportive Key Secondary Endpoints							
Time to delivery				Y			Y
Proportion of births prior to $37^{0/7}$ weeks' gestation – ascertain the GA at delivery based on a records review				Y			
Proportion of births at term ($37^{0/7}$ to $41^{6/7}$ weeks' gestation) – ascertain the GA at delivery based on a records review				Y			
Length of neonatal hospital stay – duration (in days) of neonatal hospital admission from the medical records				Y			Y
Newborn hospital readmission and length of stay							Y
Proportion of births prior to $28^{0/7}$ weeks' gestation				Y			
Proportion of births prior to $32^{0/7}$ weeks' gestation				Y			
Proportion of births prior to $35^{0/7}$ weeks' gestation				Y			
Proportion of births ≤7 days of IP administration				Y			
Proportion of births ≤48 hours of IP administration				Y			
Proportion of births ≤24 hours of IP administration				Y			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Will be presented in the integrated analysis.

Following review of the data, additional analyses maybe conducted to further support the evaluation and interpretation of the data.

8.1.2. Planned Key Secondary Efficacy Statistical Analyses

No formal statistical analysis will be performed but summary statistics will be provided.

8.1.3. Planned Other Secondary Efficacy Statistical Analyses

Other Secondary Efficacy Statistical Analysis
Endpoint
• 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 11.5.4. • Proportion of births prior to $28^{0/7}$ weeks' gestation • Proportion of births prior to $32^{0/7}$ weeks' gestation • Proportion of births prior to $35^{0/7}$ weeks' gestation • Proportion of births ≤7 days from the first study treatment • Proportion of births ≤48 hours from the first study treatment • Proportion of births ≤24 hours from the first study treatment
Results Presentation
• Data will be summarized by treatment group.

8.2. Safety Analyses

All safety summaries will be performed for the Safety Population as defined in Section 0 of this document. A listing of all safety data will be presented.

8.2.1. Overview of Planned Analyses

The safety analyses will be based on the Maternal and Neonatal Safety Populations, unless otherwise specified.

Table 5**Error! Not a valid bookmark self-reference.** provides an overview of the planned analyses with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 5 Overview of Planned Safety Analyses

Endpoints	Observed				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Exposure								
Extent of Exposure	Y			Y				
Maternal Endpoints								
Adverse Events								
All AEs	Y			Y				
Most Common AEs	Y							
Serious AEs	Y			Y				
AEs of special interest	Y			Y				
Disease-related AEs	Y			Y				
Clinical Laboratory	Y			Y	Y			Y
Maternal Vital Signs	Y			Y	Y			Y
Maternal Health Care Resource Use				Y				
Fetal Endpoints								
Adverse Events								
All AEs	Y			Y				
Most Common AEs	Y			Y				
Serious AEs	Y			Y				
AEs of special interest	Y			Y				
Fetal Heart Rate	Y			Y	Y			Y
Neonatal Endpoints								
Adverse Events								
All AEs	Y			Y				
Most Common AEs	Y			Y				
Serious AEs	Y			Y				
AEs of special interest	Y			Y				
Disease-related AEs	Y			Y				
Neonatal Health Care Resource Use				Y				
Neonatal Birth Record	Y			Y				
APGAR scores	Y			Y				

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.2.2. Extent of Exposure (Maternal)

Summaries will be presented only for mothers by initial treatment.

Duration of exposure (hour) is defined as the total number of hours a subject is exposed to any study drug and will be presented as the total number of hours from the first dose date/time (Day 1) to the last dose date/time (date/time of last dose - the date/time of first dose).

The duration of exposure to study drug by treatment will be summarized using descriptive statistics for Maternal Safety Population. The duration of exposure will then be classified into one of the following categories: 0 to ≤1 hour, >1 and ≤6 hours,>6 and ≤12 hours, >12 and ≤24 hours, >24 and ≤36 hours, >36 and ≤48 hours and >48 hours and will be presented as the number and percentage of subjects in each duration category.

The total volume administered during the infusion and the number of infusion interruptions will be summarized using descriptive statistics.

In addition, reasons for IP deviation, escalation and interruption will also be listed. Details of IP deviation will be finalized before DBF.

Also, inadequate therapeutic response will be summarized and listed.

A summary of each subject exposure will be presented in a listing.

8.2.3. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. A mapping of the MedDRA primary system organ class (SOC) and preferred term (PT) that each verbatim term has been coded to will be provided in a listing. In general, AEs will be presented in descending order from the SOC with the highest total incidence (that is, summed across all treatment groups) for any adverse event within the class to the SOC with the lowest total incidence. Within the SOC level, AEs will be presented in descending order from the PT with the highest total incidence to the PT with the lowest total incidence. If the total incidence for any two or more PTs within an SOC is equal, the PTs will be presented in alphabetical order. A PT will not be presented if no adverse events occur within the level. At each level of summarization, a subject is counted only once if the subject reported one or more events.

The number and percentage of subjects with any AE started on or after the first study treatment will be summarized by treatment group in the tables. All AEs will be listed.

8.2.3.1. All Adverse Events

The number and percentage of subjects reporting at least one AE for each SOC and PT will be reported by treatment group. The summary will include both non-serious and serious AEs. A listing of all adverse events will be provided.

The AE will be summarized by maternal, fetal and neonatal events, separately.

8.2.3.2. Relationship of Adverse Events to Study Drug

AEs by relationship to study drug (as assessed by the investigator) will be presented in listing. The investigator will provide an assessment of the relationship of the event to the study drug. The relationships are recorded as "Yes" or "No" on the CRF page. AEs that are missing a relationship will be presented with a missing relationship.

The AE will be listed by maternal, fetal and neonatal events, separately.

8.2.3.3. Most Common Adverse Events

A summary of most common on-treatment adverse events (>2% incidence rate among retosiban and placebo group) by treatment will be produced.

Most common AEs will be reported in the similar manner as all AEs.

The AE will be summarized by maternal, fetal and neonatal events, separately.

8.2.3.4. Serious Adverse Events

The seriousness of an AE should be assessed by the Investigator independently from the severity of the AE. A serious AE (SAE) is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is possible of drug-induced liver injury with hyperbilirubinemia.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

SAEs will be reported in the similar manner as all AEs. A listing of SAEs will be provided.

The SAEs will be summarized by maternal, fetal and neonatal events, separately.

8.2.3.5. Adverse Events of Special Interest

Adverse Events of Special Interest (AESIs) are AEs potentially related to treatment administration (direct or indirect) and are of special interest for evaluating and characterizing the outcomes of women, fetuses, and neonates participating in this study.

AESIs will be reported in the similar manner as all AEs. A listing of AESIs will be provided.

The AESIs will be summarized by maternal, fetal and neonatal events, separately if there are more than 3 subjects reported AESIs. If the number of subjects with AESIs is less than or equal to 3 subjects, only listings will be provided. Also, individual listing for each type of AESIs will be provided if there are any events.

Maternal, fetal and neonatal AESIs are as follows:

Maternal AESIs:

- Maternal death
- Chorioamnionitis and its complications
  - Clinical chorioamnionitis, PPROM, 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

Fetal AESIs:

- 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 AESIs:

- Neonatal death
- Asphyxia
- Infections (early onset neonatal sepsis, septic shock, pneumonia, meningitis)
- RDS
- Hypotension
- IVH/periventricular leukomalacia
- Bronchopulmonary dysplasia
- Neonatal acidosis

- Hyperbilirubinemia
- Neonatal enterocolitis
- Hypoxic ischemic encephalopathy

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

Maternal and neonatal disease-related events (DREs) described below will be reported in a similar manner as all AEs. A listing of DREs will be provided.

The DREs will be summarized by maternal and neonatal events, separately if there are more than 3 subjects with reported DREs. If the number of subjects with DREs is less than or equal to 3 subjects, only listings will be provided. Also, individual listing for each type of DREs will be provided if there are any 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 Protocol Section 7.4.1.7.2 applies
- Hospitalization for delivery, unless prolonged or 1 of the conditions listed at the end of Protocol Section 7.4.1.7.2 applies Signs and symptoms of labor discomfort (e.g., cramping, backache, muscle aches, nausea)

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 (severe)

- Vision
  - Retinopathy of prematurity (all stages)

- Auditory
  - Hearing disorder

- Other
  - Temperature instability
  - Hypoglycemia

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. However, if one or all of the following conditions apply, then the event should be reported as an AE/SAE using the standard process:

- 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.

8.2.3.7. Death

A listing of death will be provided by maternal, fetal and neonatal events, separately.

8.2.4. Health Outcome

8.2.4.1. Neonatal Health Care

Neonatal health care will be summarized using Neonatal Safety Population.

Descriptive statistics will be summarized for cumulative length of Neonatal Hospital Stay in days and log (length of Hospital Stay) for neonates at birth by treatment.

A listing of all data available for neonatal health care utilization both at birth and readmission will be provided for Neonatal Safety population.

8.2.4.2. Maternal Health Care

A listing of all data available for maternal pre-term labor related and at delivery health care resource utilization will be provided for maternal safety population.

8.2.5. Clinical Laboratory

Summaries for hematology and chemistry parameters will be performed using the Maternal Safety Population.

Summary tables presenting observed values and changes from baseline will be presented for clinical laboratory tests with numeric values by treatment group. Changes from baseline to each scheduled post-baseline visit will be presented.

The number and percentages of subjects with laboratory values below or above normal ranges for pregnant women will be summarized by treatment groups (hematology).

The subjects with potential clinically important laboratory data (hematology and chemistry) will be listed. The criteria for laboratory values outside of normal ranges are detailed in Appendix 11.8.1. If there are only the lower or upper ranges, only the lower or upper changes will be calculated for direction of interests.

8.2.6. Vital Signs

8.2.6.1. Maternal Vital Signs

Summaries for maternal vital signs will be performed using the Maternal Safety Population

Summary tables will be presented for vital sign data including weight (kg), height (cm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (°C), heart rate (beats/min), and respiration rate (breaths/minute), by treatment group. Observed results at each scheduled timepoint (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 end of the infusion), and at the face-to-face post-infusion assessment visit), will be presented. Changes from baseline to each scheduled post-baseline visit will be presented.

All maternal vital sign data below and above normal ranges will be presented in a listing. The criteria for vital signs values with potential clinical importance are detailed in Appendix 11.8.2.

8.2.6.2. Fetal Heart Rate

Summaries for fetal heart rate will be performed using the Maternal Safety Population.

A table will summarize categorical fetal heart rate results by treatment group during treatment phase and post-treatment phase. Categories to be presented are Category I, II and III based on ACOG guidelines [ACOG, 2009].

All fetal heart rate data by subject will be presented in a listing.

8.2.7. Neonatal Birth Record

Continuous variables, such as weight (g) and head circumference (cm) at neonatal birth record will be summarized. Also, APGAR at 1 and 5 minutes at birth will be summarized by reporting the number and percentage of subjects by treatment group. In addition, Neonatal Apgar scores at 1 and 5 minutes at birth will presented categorically (>=7 or <7)

All neonatal birth record data will be listed.

8.3. Pharmacokinetic Analyses

The PK concentration data will be listing for plasma, cord blood and blood milk samples.

8.4. Biomarker Analyses

fFN results and cervical length will be presented in the baseline characteristics table. Also, the results will be listed. If applicable, inflammatory biomarker such as IL-6 will be summarized and listed.

Whenever applicable, the details of these additional analyses to explore the correlation of biomarker and the study effect will be described in a separate document.

9. DEVIATION OF PLANNED ANALYSES FROM PROTOCOL

No changes will be made to the planned analyses after the breaking of the study blind; however, due to the early termination of the study and the resultant low number of subjects enrolled in the study, not all originally planned data analyses, as outlined in the protocol, will be performed.

The following changes will be made to the planned analyses from the protocol:

- The co-primary endpoints (time to delivery or treatment failure, whichever came first, and neonatal composite outcome) will not statistically analysed but will be summarized with descriptive statistics for each treatment group.

- Sample size re-estimation was not performed.

- The key secondary endpoints of time to delivery, proportion of preterm births ($<37^{0/7}$ weeks' gestation), proportion of births $\geq 37^{0/7}$ weeks' gestation, and neonatal length of hospital stay will not analysed but will be summarized with descriptive statistics for each treatment group.

- Time to delivery by preterm labor criteria (IC #4) will be summarized with descriptive statistics for each treatment group. No other subgroup analyses for the co-primary endpoints and key secondary endpoints will not be performed.

- Other exploratory covariate analyses will not be performed to examine the relationship between the treatment response and potential covariates including baseline fFN value, subclinical intrauterine infection, and other concomitant medications.

- Maternal and neonatal health outcomes will not be analysed but will be presented in data listings and analysis by subgroups will not be explored.

- Data will not be presented for neonatal ambulatory surgery as part of neonatal health care resource use results.

- No formal interim analyses will be performed.

- The PK data will be not analysed but will be listed for plasma, cord blood and blood milk samples.

- No analysis for retosiban clearance and volume of distribution and the effect of covariates on these parameters will be performed.

- Newborn hospital readmission and length of stay will not be analysed but will be listed.

- Incidence of treatment-limiting toxicities including both clinical and laboratory etiology causing subject to discontinue study treatment will not analysed.

- No analysis for Edinburgh Postnatal Depression Scale and EQ-5D-5L will be performed.

- No analysis using per-protocol (PP) population will be performed.

10. REFERENCES

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

GlaxoSmithKline Document Number 2014N194467_05: Randomized, Double-Blind, Multicenter, Phase III Study Comparing the Efficacy and Safety of Retosiban Versus Placebo for Women in Spontaneous Preterm Labor. Effective date: 20-Jun-2016

11. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 11.1	Appendix 1: Protocol Deviation Definitions
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.2	Appendix 2: Time and Events
Section 11.3	Appendix 3: Treatment States and Phases
Section 11.4	Appendix 4: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 11.5	Appendix 5: Derived and Transformed Data • General, Study Population & Safety • Efficacy
Section 11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 11.7	Appendix 7: Primary and Sensitivity Analyses for Co-Primary Endpoints with Missing Data
Section 11.8	Appendix 8: Values of Potential Clinical Importance • Laboratory Values for Pregnant Women • Vital Signs for Pregnant Women • Fetal Heart Rate
Section 11.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 11.10	Appendix 10: Abbreviations & Trade Marks
Section 11.11	Appendix 11: List of Data Displays

11.1. Appendix 1: Protocol Deviation Definitions

Subject compliance to the protocol will be evaluated prior to database freeze and unblinding the study and subjects with significant protocol deviations will be identified. Specific criteria for what constitutes a major protocol violation will be determined by the study team and the following criteria will be considered:

Maternal Major Protocol Violation

- Not meeting inclusion criteria 3 (Gestational age between $24^{0/7}$ and $33^{6/7}$ weeks as determined by (1) known fertilization date, either in vitro fertilization or intrauterine insemination or (2) a best estimated due date confirmed or established by the earliest ultrasound performed before $24^{0/7}$ weeks gestation.)

11.2. Appendix 2: Time and Events

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

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

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

Procedures	Screening Phase	Inpatient Randomized Treatment Phase		Post-Infusion Assessment Phase[1]		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	1-week face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery[2]	Delivery to 28 days post EDD	
Health Outcome Assessments									
Maternal and neonatal health care resource use[21]						X		X	
Pharmacokinetic Assessments									
Maternal PK blood sample[22]		X[21] ◄——► X							
Cord blood sample[23]						X			
Breast milk/colostrum sample[24]						X			
Genetic and Biomarker Assessments									
Genetic blood sample for maternal DNA[25]	X								
Biomarker maternal blood sample[26]	X								
Genetic blood sample for cell-free fetal DNA[27]	X								
Other Assessments									
Fetal fibronectin (optional)[28]	X								
Cervical length via transvaginal ultrasound (optional)[29]	X								
Confirm no other study participation for infant[30]								X	

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

1. Subjects who remain undelivered after 48 hours will return for a face-to-face post-infusion visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase. The subject will then be contacted every week via telephone to determine and record if she has delivered or experienced any subsequent episodes of preterm labor. Note: If the subject is scheduled to visit the clinic for reasons not required by this protocol and/or she happens to be present at the time the telephone assessment is due, this assessment may be completed face-to-face.
2. During the Maternal Post Delivery Assessment Phase, subjects will be contacted by telephone within 6 weeks of delivery for a post-delivery assessment, including an assessment of AEs (±2 weeks), status of breastfeeding (±2 weeks), and completion of the EPDS (±6 weeks).
3. Prestudy screening information that is collected by the study site may need to come from records that are obtained before the subject has signed the informed consent. The subject will be required to provide written informed consent before any study-specific procedures are performed, and the consent will request permission for use of any information collected prior to its having been signed.
4. During the study, the subject or other legal guardian for the infant (both delivered and undelivered) will be asked to give consent for the infant to participate in a separate long-term infant follow-up study for safety and neurodevelopment. Withdrawal from the study after beginning randomized treatment or discontinuing IP does not preclude involvement in the infant follow-up study.
5. Medical history will be collected at Screening. If a condition with a start date predating Day 0 (Screening) is subsequently discovered, the condition should be recorded in the Medical History eCRF. For obstetrics history, the investigator will make every effort to obtain this information either via computer records, directly from the subject's primary care obstetrician, or via telephone. However, in cases in which these records are not readily available (e.g., off hours, holiday), the investigator can use gestational age based on the verbal history from the subject with the intent of getting confirmation from the medical records or from the subject's primary care obstetrician as soon as possible.
6. The urine drug screen will be performed using a point-of-care qualitative testing device. A point-of-care breath analyzer for alcohol will be used in some countries in addition to the urine drug screen.
7. A cervical examination (including dilation, effacement, and station) will occur at Screening, and an additional cervical examination may be performed before dosing based on investigator discretion. If a predosing cervical examination reveals dilation >4 cm, the subject cannot be dosed. Additional cervical examinations (Day 1, Day 2, and/or at the 1-week face-to-face post-infusion assessment visit) will be performed based on investigator discretion.
8. The abdominal ultrasound for determination of the AFI will be performed at Screening for all subjects.
9. Uterine tocography or manual palpation (if necessary) will be performed prior to dosing to confirm persistent uterine contractions. If the examination reveals in the 60 minutes before IP dosing a rate that is <4 contractions of a least 30 seconds' duration over a 30-minute interval, the subject cannot be dosed. Manual palpations will be permitted if there are technical challenges with measuring contraction frequency.
10. If not previously administered, antenatal corticosteroid treatment should be administered as either (1) two 12-mg doses of betamethasone given intramuscularly 24 hours apart or (2) four 6-mg doses of dexamethasone administered intramuscularly every 12 hours. A single rescue course of antenatal corticosteroids is permitted if the antecedent treatment was at least 7 days prior to study enrollment. Investigators have discretion to use a standardized regimen of magnesium sulfate, as well as intrapartum antibiotic prophylaxis for perinatal group B streptococcal infection.
11. Information regarding delivery will be obtained through a review of the hospital and medical records. Growth parameters include neonatal weight, length, and head circumference.
12. A 12-lead ECG will be performed prior to dosing. If the results are interpreted by the investigator to have clinically significant abnormalities, the subject cannot be dosed.
13. Blood pressure, pulse rate, respiratory rate, and temperature will be assessed at Screening, as part of maternal safety monitoring during the Inpatient Randomized Treatment Phase, and at the post-infusion assessment visit. During the Inpatient Randomized Treatment Phase, vital signs and oxygen saturation will be assessed and recorded within the following windows relative to the start of the infusion: 15 to 30 minutes, 4 to 8 hours, 20 to 24 hours, at the end of the infusion, at the time of any dose changes, and as warranted by a medical condition. Oxygen saturation less than 92% should be recorded as an AE or SAE, as appropriate.
14. Maternal subjects will complete the Edinburgh Postnatal Depression Scale, a self-reported questionnaire, at the maternal follow-up assessment 6 weeks (±6 weeks) after delivery.

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

11.3. Appendix 3: Treatment States and Phases

Study treatment start date/time and/or stop date/time are determined by the infusion of IP administered.

11.3.1. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to study treatment, unless otherwise specified.

Treatment Phase	Definition
Pre-treatment	Date/Time < Initial Study Treatment Start Date/Time
On-treatment	Study Treatment Start Date Time ≤ Date Time ≤ Study Treatment Stop Date Time + 12 hours
Post-treatment	Date/Time > Study Treatment Stop Date/Time + 12 hours

11.3.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date/time of the study treatment.

11.3.3. Treatment States for AE Data

Treatment State	Definition
AE = Pre-treatment	AE Start Date < Study Treatment Start Date
AE = On-treatment	If AE onset date is on or after the treatment start date and on or before the treatment stop date. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1
AE = Post-treatment	If AE onset date is after the treatment stop date. AE Start Date > Study Treatment Stop Date + 1
AE Onset Time Since 1st Dose (Days)	If Study Treatment Start Date > AE Onset Date : **= AE Onset Date – Study Treatment Start Date** If Treatment Start Date ≤ AE Onset Date : **= AE Onset Date – Study Treatment Start Date + 1** Missing otherwise
AE Duration (Days)	**AE Resolution Date – AE Onset Date + 1**
AE = Drug-related	If relationship is marked 'YES' on [Inform/CRF OR value is missing.

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment if there are no post-infusion assessments and delivery.

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. Study Treatment & Sub-group Display Descriptors

Study Treatment Descriptions		
Code	**Description**	**Order of Table Presentation**
1	Retosiban	2
2	Placebo	1

11.4.2. Baseline Definition & Derivations

11.4.2.1. Baseline Definitions

For all endpoints (expect as noted) baseline value will be the latest pre-dose assessment.

Parameter	Study Assessments Considered As Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre Dose)	
Safety			
Vital Signs	X	X	Last value to prior to start of IP
Laboratory	X		Screening

11.4.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline

NOTE :

- Unless otherwise specified, the baseline definitions specified in 11.4.2.1Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data are missing no derivation will be performed and baseline value will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

The baseline is defined as last assessment prior of start of IP administration. The value will be missing if the baseline data are missing. For lab parameters, last assessment prior to IP will be used as baseline if there are multiple assessment at screening or day 1.

11.4.3. Reporting Process & Standards

Reporting Process
Software
• The currently supported versions of SAS software will be used to perform all data analyses, generate tables, figures, and listings.
Reporting Area
Analysis Datasets
• Analysis datasets will be created according to ADaM implementation guide version xx. • RTF files will be generated. • All datasets are CDISC compliance.

Reporting Standards
General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated:
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• For study population and efficacy analyses, all data will be reported according to the planned treatment the subject was randomized unless otherwise stated. • For safety analyses, all data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.

Planned and Actual Time	

• Reporting for tables, figures and formal statistical analyses :
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.
• Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	

Unscheduled Visits	
• Unscheduled visits will not be included in by-visit summary tables or figures except 'any visit post-baseline category', unless otherwise stated. • All unscheduled visits will be listed.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

11.5. Appendix 5: Derived and Transformed Data

11.5.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • For laboratory assessment and vital signs' descriptive summary statistics and other endpoints, if there are multiple assessments within a same scheduled visit, the last assessment within the visit will be used. • For laboratory assessment and vital signs with potential clinical importance, if there are two values within a time window, the worst value (i.e. the most extreme value from the normal range) will be used. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. Unscheduled visit will be included. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day
• Calculated as the number of days from the first study treatment date : [1] Ref Date = Missing → Study Day = Missing (none displayed) [2] Ref Date < First Study Treatment Date → Study Day = Ref Date – First Study Treatment Date [3] Ref Data ≥ First Study Treatment Date → Study Day = Ref Date – (First Study Treatment Date) + 1

11.5.2. Study Population

Demographics
Age for Mother
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: [1] Date of birth of any subject will have this imputed as '30th June'. [2] If a subject is recorded as an adolescence in CRF and imputed date of birth in [1] is > 18 years old, the last possible date to be 18 years old will be assigned. For example, an adolescence's randomization date is 30Jun2016 and birth year is 1998. Imputed date of birth in [1] is 30Jun1998 and age is 19 years old. Then 29Jun1998 will be used as birth date to keep the subject in adolescence category. • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height (m)]^2

Extent of Exposure
• Number of hours of exposure to study drug will be calculated using dates from the trial medication form. The duration of exposure in days will be based on the formula:

Duration of Exposure in Hours = (Treatment Stop Date/Time (in minutes) – Start Date/Time (in minutes))/60

- If there are any treatment interruption during the study, then the exposure data will be adjusted accordingly.

11.5.3. Safety

Laboratory Parameters

- If a laboratory value, which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x ' becomes x - 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x - 1.
- If there is more than one value of a particular parameter for a subject for a visit, the last assessment will be used in summary; all values will be listed.

11.5.4. Efficacy

Calculation of Time to Delivery and Time to Delivery or Treatment Failure

- Once delivery is confirmed, the maternal delivery and hospitalization records will be reviewed for data collection by the investigator obstetrician. The time to delivery is calculated as the days between the delivery and start time of the infusion of IP using the formula below:
  Time to delivery (days) = (date/time of delivery – date/time of start of infusion)/(24*60)
  The exact date/time of delivery and infusion will be used to determine the time to delivery.
- Time to delivery or treatment failure is defined as the days between the delivery or treatment failure and start time of the infusion of IP in a similar fashion to the time to delivery.

Calculation of Neonatal Composite Endpoint

Neonatal Composite Endpoint

The presence of any of the following endpoints determined from review of medical records will lead to a value of 1 for the neonatal composite endpoint and 0 otherwise:

- Fetal or neonatal death
- Respiratory Distress Syndrome (RDS)
  - Requiring continuous positive airway pressure or mechanical ventilation. Diagnosis requires a chest radiograph consistent with RDS (reticulogranular appearance to the lung fields or air bronchograms) within the first 24 hours of life

    OR

  - Received surfactant for a clinical picture of RDS within the first 24 hours of life
- Bronchopulmonary dysplasia at ≥36 weeks postmenstrual age (determined by adding chronological age to GA at delivery), defined as follows:
  - >21% supplemental oxygen requirement

    OR

  - Use of high flow nasal cannula at ≥1 L (21% oxygen)
- Necrotizing enterocolitis or isolated perforation
  - Diagnosed by radiographic evidence of Stage II or higher according to Bell's staging criteria (fixed/unchanging bowel loops, pneumatosis intestinalis, portal venous gas, pneumoperitoneum)

    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 5

OR

- Requiring surgical treatment with laser or other surgical intervention including cryotherapy or treatment with anti-VEGF (vascular endothelial growth factor)

- Intraventricular Hemorrhage (IVH)
  - Grade 3 or 4 (severe IVH)

  OR

  - Any grade of IVH with posthemorrhagic hydrocephalus requiring a shunt
- White matter injury, documented on cranial ultrasound or magnetic resonance imaging, as indicated by the following:
  - Multiple cystic lucencies in periventricular white matter (may be bilateral or unilateral, may vary in size, and be diffuse or focal in distribution)

  OR

  - Porencephalic cyst (not including subependymal or choroid plexus cysts)

  OR

  - Persistent ventriculomegaly, moderate to severe

- Cerebellar hemorrhage (unilateral or bilateral)

Individual Neonatal Composite Endpoint

- This will be derived for all the conditions included under the composite endpoint. For each individual condition, the variable will be 1 if the condition is satisfied, otherwise, 0.

Neonatal Composite Endpoint without RDS

- Same as the composite endpoint without the RDS condition.

Neonatal Composite Endpoint without RDS and mortality

- Same as the composite endpoint without the RDS and fetal/neonatal death conditions.

Modified Neonatal Composite Endpoint

- Same as the composite endpoint and include the all reported neonatal events. For example, a subject is considered as experience a RDS even without record of CPAP, ventilation or Surfactant. .

Calculation of Gestational Age at Birth and Proportion of Pre-term Births

- Gestational age at birth (weeks) is defined as the gestational age when the baby is born and is captured in the eCRF. If the data are missing, the GA at birth can be calculated as follows:

  GA at Birth (weeks) = (GA at Randomization x 7 + Time to delivery) / 7

  GA at randomization will be converted to 1 decimal place (i.e. 30.2 weeks GA at randomization) prior the calculation.

- Proportion of births prior to $37^{0/7}$, $35^{0/7}$, $32^{0/7}$, or $28^{0/7}$ week's gestation (preterm)

  Subjects are considered to have delivered prior to $37^{0/7}$ weeks if the gestational age at birth is less than $37^{0/7}$ weeks (e.g.: < 37.0 weeks). Other proportions also will be calculated in a similar fashion. For proportion of births prior to $32^{0/7}$ and $28^{0/7}$ week's gestation, only mothers who were randomized prior to $32^{0/7}$ and $28^{0/7}$ week's gestation will be included respectively.

- Proportion of births at term (≥ $37^{0/7}$ week's gestation)

  Subjects are considered to have delivered at term if the gestational age is ≥ $37^{0/7}$ (e.g., ≥ 37.0 weeks)

Calculation of 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. The length of stay is calculated as the days between the delivery date/time and discharge date/time.
- 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 and reported.

11.6. Appendix 6: Premature Withdrawals & Handling of Missing Data

11.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion status was defined as subjects who either prematurely withdrawn. • Those subjects that are randomized and not dosed are not considered as prematurely withdrawn. • Subjects who are withdrawn from study participation after starting randomized treatment will not be replaced. • 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.

11.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : [1] These data will be indicated by the use of a "blank" in subject listing displays. [2] Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

11.6.2.1. Handling of Missing Stratification

Element	Reporting Detail
GA at Randomization	• If GA at randomization in weeks/days obtained from CRF is missing, the upper bound of the GA strata assigned at randomization will be used as a numeric value. For example, a subject in 24 $^{0/7}$ to 25 $^{6/7}$ group, 25 weeks and 6 days will be converted into numeric value.
Established Progesterone Use	• Established progesterone use will be derived using mediations which are taken prior to the study treatment and recorded in obstetrical medications CRF page. If a subject is stratified as progesterone user at the randomization but no progesterone medication prior to the study treatment was recorded in obstetrical medications CRF page, the subject will be considered as established progesterone user for analysis.

11.6.2.2. Handling of Missing/Partial Dates

Element	Reporting Detail

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Concomitant Medication	Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. In the case of a missing year, the year will be assumed to be the year part of informed consent date of that subject. In the case of a completely missing start date, the start date will be assumed to be prior to date of the first administration of study medication. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. In the case of a completely missing stop date, the medication will be assumed to be ongoing.
Time to Delivery and Time to Delivery or Treatment Failure	For the delivery and delivery or failure date/time, • Missing data with respect to time to delivery and time to delivery or treatment failure endpoints is unlikely to occur. If it occurs and the dates are missing, the last assessment date of a mother prior to delivery phase will be used. • If the times are missing, a "00:00" will be used for the time.
Length of neonatal hospital stay	• For neonates have the data of hospital stay at birth, if date/time of hospital admission is not missing but date/time of discharge is missing, the date/time of discharge will be imputed using EDD + 28 days in calculation of length of stay.
Adverse Events (General)	• If the dates are missing for on-treatment, or post-treatment AEs, imputation of AE dates may be performed if needed. The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied. • There will be no imputation for AE data listings
Adverse Events (Mother)	• Any partial dates for adverse events will be flagged to data management. If the full date cannot be ascertained, the following assumptions will be made whether the AE occurred on-treatment or post- treatment :

Start Date	• If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. o For AEs which can occur only during or after labor/delivery (ex. postpartum hemorrhage), if these results in a date are prior to the delivery date, then the delivery date will be assumed to be the start date. Applicable AEs will be identified by PPD/GSK medical monitor. o For other AEs that occur prior to labor or delivery, if these results in a date are prior to the first study treatment date, then the first study treatment date will be assumed to be the start date. • The AE will then be considered to start on-treatment (worst case).

<table>
<tr><th>Element</th><th colspan="2">Reporting Detail</th></tr>
<tr><td></td><td>End Date</td><td>• If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
o For AEs which can occur only during the pregnancy (ex. gestational diabetes), if these results in a date are after the delivery date, then the delivery date will be assumed to be the end date. Applicable AEs will be identified by PPD/GSK medical monitor.
o For other AEs that occur only during or after labor/delivery, if these results in a date are after the last assessment date or contact date, then the last assessment date or contact date will be assumed to be the end date.</td></tr>
<tr><td>Adverse Events (Neonate)</td><td colspan="2">• Any partial dates for adverse events will be flagged to data management. If the full date cannot be ascertained, the following assumptions will be made:</td></tr>
<tr><td></td><td>Start Date</td><td>• If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month.
• However, if these results in a date are prior to the birth date, then the birth date will be assumed to be the start date.
• The AE will then be considered to start on-treatment (worst case).</td></tr>
<tr><td></td><td>End Date</td><td>• If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
• If these results in a date are after neonatal death date, then neonatal death date will be assumed to be the end date.
• If the dates are after the last assessment date or contact date, then the last assessment date in medical record or contact date will be assumed to be the end date.
• However, if these results in a date are more than 28 days after EDD, then 28 days after EDD will be assumed to be the end date.</td></tr>
<tr><td>Adverse Events (Fetus)</td><td colspan="2">• Any partial dates for adverse events will be flagged to data management. If the full date cannot be ascertained, the following assumptions will be made:</td></tr>
<tr><td></td><td>Start Date</td><td>• If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month.
• However, if these results in a date are prior to the first study treatment date, then the first study treatment date will be assumed to be the start date.
• The AE will then be considered to start on-treatment (worst</td></tr>
</table>

Element	Reporting Detail	
		case).
	End Date	• If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • However, if these results in a date are after the birth date or fetal death date, then the birth date or fetal death date will be assumed to be the end date.

11.7. Appendix 7: Primary and Sensitivity Analyses for Co-Primary Endpoints with Missing Data

11.7.1. Co-Primary Endpoints with Missing Data

Missing data will not be imputed for primary and sensitivity analyses for co-primary endpoints.

11.8. Appendix 8: Values of Potential Clinical Importance

11.8.1. Laboratory Values for Pregnant Women

For laboratory parameters not listed below, the normal range defined in Quest will be used for analysis.

Haematology			
Laboratory Parameter	**SI Units**	**Normal Range**	
		Low Flag (< x)	**High Flag (>x)**
Eosinophils	GI/L	0	0.6
Hematocrit	1	0.28	
Hemoglobin	G/L	95	
Lymphocytes, Abs	GI/L	1.0	3.6
Lymphocytes	%	16	46
Total Neutrophil, Abs	GI/L	3.9	13.1
Platelet Count	GI/L	146	
Red Blood Cell Count (RBC)	TI/L	12.7	15.3
While Blood Cell Count (WBC)	GI/L	5.9	16.9

Clinical Chemistry			
Laboratory Parameter	**SI Units**	**Normal Range**	
		Low Flag (< x)	**High Flag (>x)**
Alanine transaminase (ALT)	U/L		25
Aspartate transaminase (AST)	U/L		32
Albumin	G/L	23	42
Bilirubin, total	UMOL/L		18.8
Chloride	MMOL/L	97	109
CO2 CONTENT	MMOL/L	20	32
Creatinine	UMOL/L		68.6
Glucose	MMOL/L	3.9	10
Magnesium	MMOL/L	0.45	0.90

Clinical Chemistry			
Laboratory Parameter	**SI Units**	**Normal Range**	
		Low Flag (< x)	**High Flag (>x)**
Phosphorus, INORG	MMOL/L	0.90	1.49
Potassium	MMOL/L	3.3	5.1
Sodium	MMOL/L	130	
Uric acid	UMOL/L		375

11.8.2. Vital Signs for Pregnant Women

Vital Sign Parameter (Absolute)	**Units**	**Clinical Concern Range**	
		Lower	**Upper**
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

11.8.3. Fetal Heart Rate

Parameter (Absolute)	**Units**	**Clinical Concern Range**	
		Lower	**Upper**
Heart Rate	bpm	< 110	> 160

11.9. Appendix 9: Model Checking and Diagnostics for Statistical Analyses

Endpoint(s)	• Length of hospital stay
Analysis	• Analysis of Covariance for the Length of hospital stay
• Length of hospital stay will be log-transformed prior to the model fitting.	

11.10. Appendix 10: Abbreviations & Trade Marks

11.10.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
AFI	Aniotic Fluid Index
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
BMI	Body mass index
BPM	Beat Per Minute
CI	Confidence Interval
CSR	Clinical Study Report
DRE	Disease-related Event
eCRF	electronic Case Report Form
EDD	Estimated Date of Delivery
EM	Expectation-maximization
EP	Established Progesterone Use
EPDS	Edinburgh Postnatal Depression Scale
EQ-5D-5L	EuroQol 5-dimensional 5-level
fFN	fetal Fibronectin
FMM	Finite Mixture Models
GA	Gestational Age
GSK	GlaxoSmithKline
HR	Heart rate
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IP	Investigational Product
ITT	Intent-to-treat
Kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Description
NICU	Neonatal Intensive Care Unit
PK	Pharmacokinetic
PP	
PPROM	Preterm Premature Rupture of Membranes
RAP	Reporting and Analysis Plan
RDS	Respiratory Distress Syndrome
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SI	System Independent
SD	Standard deviation
SDTM	Study Data Tabulation Model
SOP	Standard Operating Procedure
TRT	Treatment
ULN	Upper limit of normal

11.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS
WinNonlin

11.11. Appendix 11: List of Data Displays

A separate document for shells contains all table, listing and figures' (TLFs) for the planned final analysis. However, due to early termination of the study, only TLFs listed in this appendix will be generated.

11.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables
Study Population	1.01 to 1.xx
Efficacy	2.01 to 2.xx
Safety	3.01 to 3.xx
Other Analysis	
Section	**Listings**
ICH Listings	1 to 200
Other Listings	From 201

11.11.2. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.01	All Randomized		Summary of Subject Disposition		
1.03	Maternal ITT		Summary of Significant Protocol Deviations		
Demographics					
1.11	Maternal ITT		Summary of Maternal/Fetal Demographic		
1.12	Maternal ITT		Summary of Maternal/Fetal Baseline Characteristics		
1.13	Neonatal ITT		Summary of Neonatal Birth Data		
1.15	Maternal ITT		Summary of Maternal Race and Racial Combinations		
Medical Condition & Con Meds					
1.23	Maternal ITT		Summary of Obstetrical History		
1.24	Maternal ITT		Summary of Prenatal History		
1.29	Maternal ITT		Summary of Maternal Obstetrical Medications		
1.30	Maternal ITT		Summary of Maternal Magnesium Sulfate		
1.31	Maternal ITT		Summary of Maternal Antenatal Corticosteroids		

11.11.3. Efficacy Tables

Efficacy Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Time to Delivery					
2.01	Maternal ITT		Summary of Time to Delivery		
2.02	Maternal ITT		Summary of Time to Delivery or Treatment Failure		
2.53	Maternal ITT		Summary Statistics for Time to Delivery by Preterm Labor Criteria (IC #4)		
Neonatal Composite Endpoint					
2.101	Neonatal ITT		Proportion of Neonatal Composite Endpoint		
2.102	Neonatal ITT		Proportion of Modified Neonatal Composite Endpoint		
Proportion of Births					
2.181	Maternal ITT		Proportion of Births		
Neonatal Hospital Admission: Length of Neonatal Hospital Stay					
2.301	Neonatal ITT		Summary of Neonatal Hospital Stay		

11.11.4. Safety Tables

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.01	Maternal Safety		Summary of Extent of Study Drug Exposure		
3.02	Maternal Safety		Summary of Inadequate Therapeutic Response		
Maternal Adverse Events					
3.11	Maternal Safety		Summary of Maternal Adverse Events		
3.41	Maternal Safety		Summary of Most Common Maternal Adverse Events		
3.51	Maternal Safety		Summary of Maternal Serious Adverse Events		
Fetal Adverse Events					
3.111	Maternal Safety		Summary of Fetal Adverse Events		
3.141	Maternal Safety		Summary of Most Common Fetal Adverse Events		
3.151	Maternal Safety		Summary of Fetal Serious Adverse Events		

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.171	Maternal Safety		Summary of Fetal Adverse Events of Special Interest		
Neonatal Adverse Events					
3.211	Neonatal Safety		Summary of Neonatal Adverse Events		
3.241	Neonatal Safety		Summary of Most Common Neonatal Adverse Events		
3.251	Neonatal Safety		Summary of Neonatal Serious Adverse Events		
3.271	Neonatal Safety		Summary of Neonatal Adverse Events of Special Interest		
3.281	Neonatal Safety		Summary of Neonatal Disease-Related Adverse Events		
Labs					
3.401	Maternal Safety		Summary of Observed Value and Change from Baseline in Hematology by Visit		
3.402	Maternal Safety		Summary of Hematology Results Outside the Reference Ranges by Visit		
3.403	Maternal Safety		Summary of Observed Value and Change from Baseline in Clinical Chemistry by Visit		

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
3.421	Maternal Safety		Summary of Observed Value and Change from Baseline in Maternal Vital Signs by Visit		
3.424	Maternal Safety		Summary of Fetal Heart Rate Category		

11.11.5. ICH Listings

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Randomization					
1	All Randomized		Randomised and Actual Treatments		
8	All Randomized		Randomised and Actual Treatments by Center		
9	All Randomized		Randomised and Actual Treatments by Center for Subjects not Enrolled in ARIOS at Study Completion		
Subject Disposition					
2	All Randomized		Reasons for Study Withdrawal		
3	All Randomized		Reasons for Study Treatment Discontinuation		
4	All Randomized		Study Disposition		
5	All Randomized		Significant Protocol Deviations		
Demographics					
11	Maternal ITT		Maternal Demographic Characteristics		
12	Maternal ITT		Maternal Baseline Characteristics I		
13	Maternal ITT		Maternal Baseline Characteristics II		

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
14	Maternal ITT		Maternal Race		
15	Neonatal ITT		Neonatal Birth Data		
Exposure					
21	Maternal Safety		Study Drug Exposure		
30	Maternal Safety		Inadequate Therapeutic Response		
Medical Condition & Con Meds					
23	Maternal ITT		Prior and Concomitant Medications		
24	Maternal ITT		Obstetrical Medications		
25	Maternal ITT		Magnesium Sulfate		
26	Neonatal ITT		Antenatal Corticosteroids		

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
41	Maternal Safety		All Maternal Adverse Events		
42	Maternal Safety		Maternal Serious Adverse Events		
43	Maternal Safety		Maternal Adverse Events of Special Interest		
44	Maternal Safety		Maternal Adverse Events of Special Interest: Chorioamnionitis		
56	Maternal Safety		Fetal Adverse Events of Special Interest: Category II-III FHR Event		
57	Maternal Safety		Maternal Disease-Related Adverse Events		
62	Maternal Safety		Maternal Deaths		
76	Maternal Safety		All Fetal Adverse Events		
77	Maternal Safety		Fetal Serious Adverse Events		
78	Maternal Safety		Fetal Adverse Events of Special Interest		
79	Maternal Safety		Fetal Deaths		
82	Neonatal Safety		All Neonatal Adverse Events		
83	Neonatal Safety		Neonatal Serious Adverse Events		

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
84	Neonatal Safety		Neonatal Adverse Events of Special Interest		
86	Neonatal Safety		Neonatal Adverse Events of Special Interest: Respiratory Distress Syndrome		
87	Neonatal Safety		Neonatal Adverse Events of Special Interest: Hypotension		
89	Neonatal Safety		Neonatal Adverse Events of Special Interest: Intraventricular Hemorrhage		
90	Neonatal Safety		Neonatal Adverse Events of Special Interest: Bronchopulmonary Dysplasia		
92	Neonatal Safety		Neonatal Adverse Events of Special Interest: Hyperbilirubinemia		
93	Neonatal Safety		Neonatal Adverse Events of Special Interest: Infant Infections Event		
96	Neonatal Safety		Neonatal Disease-Related Adverse Events		
97	Neonatal Safety		Neonatal Deaths		
108	Neonatal Safety		Neonatal Disease-Related Adverse Events: Hydrocephalus		
111	Neonatal Safety		Neonatal Disease-Related Adverse Events: Retinopathy of Prematurity		

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
LABS					
113	Maternal Safety		Haematology Laboratory Data Outside the Reference Ranges		
116	Maternal Safety		Clinical Chemistry Laboratory Data Outside the Reference Ranges		
Vital Signs					
121	Maternal Safety		Vital Signs for Subjects with Abnormalities of Potential Clinical Importance		
123	Maternal Safety		Fetal Heart Rate		

11.11.6. Non-ICH Listings

Non-ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Screening Visit					
203	All		Obstetrical History at Screening		
204	All		Prenatal History at Screening		
Efficacy					
301	Maternal ITT		Time to Delivery or Treatment Failure		
302	Neonatal ITT		Neonatal Composite Endpoints		
303	Neonatal ITT		Neonatal Health Care Resource Utilization at Birth		
304	Neonatal ITT		Neonatal Heath Care Resource Utilization at Readmission		
309	Neonatal ITT		Modified Neonatal Composite Endpoints		
Safety					
403	Maternal Safety		Maternal Health Care Resource Utilisation (In-patient)		

Non-ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
407	Maternal Safety		Subsequent Preterm Labor		
PK					
461	Maternal Safety		Retosiban Concentration in Plasma		
462	Maternal Safety		Retosiban concentration in Umbilical Cord Blood		
463	Maternal Safety		Retosiban concentration in Breast Milk		