Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan

Title	:	Randomized, Double-blind, Multicenter, Phase III Study Comparing the Efficacy and Safety of Retosiban Versus Atosiban Therapy for Women in Spontaneous Preterm Labor
Compound Number	:	GSK221149
Effective Date	:	04-OCT-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 200721.
- 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.

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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 200721.
Protocol	• This RAP is based on the original protocol (Dated: 14-May-2014), country-specific amendment 02 (France; dated 29-Jan-2015, country-specific amendment 02 (United Kingdom; dated 29-Jan-2015) and country-specific amendment 03 (Sweden; dated 04-Feb-2015), protocol amendment 04 (Dated: 22-Aug-2016), and protocol amendment 05 (Dated: 21-Dec-2016) for study GSK200721 [GlaxoSmithKline Document Numbers: 2014N194185_00, 2014N194185_01, 2014N194185_02, 2014N194185_03, 2014N194185_04 and 2014N194185_05].
Primary Objective	• Demonstrate the superiority of retosiban to prolong pregnancy compared with atosiban.
Primary Endpoint	• Time to delivery (in days) from the start of investigational product (IP) administration until delivery, based on a records review.
Study Design	• Phase III, randomized, double-blind, double-dummy, 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 97 patients and patients were randomly assigned to one active arm (retosiban) and one active control arm (atosiban).
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	• The study is designed to test the following hypotheses: o Null hypothesis: The prolongation of pregnancy as measured by time to delivery is equal between the women randomized to retosiban versus atosiban. o Alternative hypothesis: The prolongation of pregnancy as measured by time to delivery is unequal between the women randomized to retosiban versus atosiban.

Primary Analyses	• Time to delivery will be analyzed using a two-component normal mixture model, where the components pertain to women who deliver imminently and to women who deliver at term. The exact weight of each component will be determined by the observations from the component and model concomitant variables including treatment and Gestational Age (GA) at randomization. Within each component, the expected time to delivery will be modeled as a function of treatment as fixed effect and GA at randomization and established progesterone use (yes or no) as a covariate. Comparison of the two treatments will be performed through mean point estimates and their corresponding 95% confidence intervals derived from the finite mixture model.
Secondary Analyses	• Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. • Key secondary efficacy endpoints such as proportion of births prior to $37^{0/7}$ weeks' gestation, proportion of births at term ($37^{0/7}$ to $41^{6/7}$ weeks' gestation) and the neonatal composite endpoint will be analyzed using logistic regression models to facilitate comparison between the two treatments. • Key secondary efficacy endpoint length of neonatal hospital stay will be log-transformed prior to analysis. Log-transformed length of hospital stay will be analyzed using an analysis of covariance model adjusting for the covariates of GA at randomization and established progesterone use (yes or no). Other covariates may be added appropriate. The model-adjusted length of stay will be presented for each treatment group. • Binary secondary analysis endpoints will be analyzed in a similar fashion to the neonatal composite analysis. Binary exploratory endpoints will be analyzed in a similar fashion to the key secondary endpoints. The details of analyses are provided in the body of the RAP.

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)

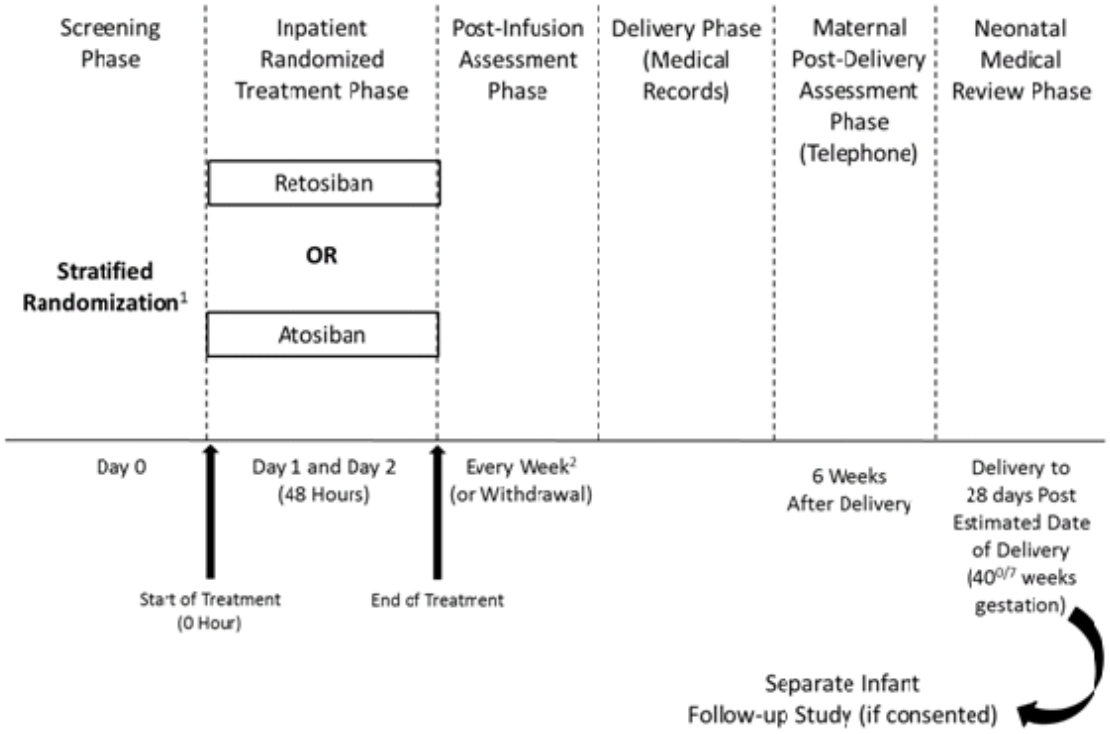
Objectives	Endpoints
Primary	**Primary**
• To demonstrate the superiority of retosiban to prolong pregnancy compared with atosiban.	• Time to delivery from the start of IP administration until delivery, based on a records review.
Secondary	**Secondary**
• To describe the outcomes of nwborns during the neonatal period (through 28 days post estimated date of delivery [EDD]) for retosiban compared with atosiban.	<u>Key Secondary Endpoints</u> • Proportion of births prior to $37^{0/7}$ weeks' gestation – ascertain the GA at delivery based on a record review • Proportion of births at term ($37^{0/7}$ to $41^{6/7}$ weeks' gestation) – ascertain the GA at delivery based on a record review • Length of neonatal hospital stay – confirm duration (in days) of neonatal hospital admission from the medical records • Proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite determined up to 28 days after estimated date of delivery (EDD) (of $40^{0/7}$ weeks) <u>Other Secondary Endpoints</u> • Proportion of neonates with any of the composite neonatal morbidity and mortality excluding Respiratory Distress Syndrome (RDS) • 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
• To describe the maternal, fetal, and neonatal safety profile during and after IV retosiban treatment compared with atosiban treatment.	<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 atosiban on health care resource use and patient-reported outcomes associated with the maternal and	• Maternal hospital admission (e.g., length of stay, hospital unit and type) and resource use (e.g., use of transport services, admission to extended stay facility) • Neonatal interventions of interest (e.g., parenteral nutrition, surfactants, blood products), procedures (e.g., imaging, such as ultrasound, computed tomography,

Objectives	Endpoints
neonatal hospitalization.	etc.), and surgical procedures. •
• To obtain further data on the pharmacokinetics of retosiban in pregnant women, including the effect of covariates such as age, weight, race/ethnicity, and GA on retosiban clearance and volume of distribution.	• Retosiban concentration in plasma, cord blood and breast milk. • Population PK analysis is not performed in the protocol.

2.3. Study Design

Overview of Study Design and Key Features



1. Stratification (1:1) to retosiban or atosiban based on established progesterone therapy at Screening (subjects on established progesterone therapy versus subjects not on established progesterone therapy) and gestational age ($24^{0/7}$ to $25^{6/7}$; $26^{0/7}$ to $27^{6/7}$; $28^{0/7}$ to $30^{6/7}$; $31^{0/7}$ to $33^{6/7}$)
2. Subjects who have not delivered after 48 hours will return for a face-to-face post-infusion assessment visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) after the Inpatient Randomized Treatment Phase. The subject will then be contacted every week via telephone to determine and record if she has delivered or if she has experienced any subsequent episodes of preterm labor. Retreatment with the investigational product (retosiban or atosiban) is allowed.

Overview of Key Study Design Features	
Design Features:	• Phase III, randomized, double-blind, double-dummy, multicenter design • Subjects are females, aged 18 to 45 years (Sweden) or aged 12 to 45 years (all other countries including UK, Germany, Italy, Israel, South Korea, Belgium, Mexico, Spain and Brazil), 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. • Atosiban will be given intravenously in 3 successive stages: an initial bolus dose of 6.75 mg using atosiban 6.75 mg/0.9 mL solution for injection, immediately followed by a continuous high dose infusion at 18 mg/hour for 3 hours, then a lower 6 mg/hour infusion for the remainder of the 48-hour treatment period using the atosiban 37.5 mg/5 mL concentrate for solution.
Treatment Assignment:	• A total of 97 patients were blindly randomly assigned to retosiban or atosiban 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 will be randomly assigned in 1:1 ratio to receive either retosiban or atosiban using an IVRS in accordance with the randomization schedule.
Interim Analysis	• There study was terminated before inteirm analysis due to feasibility. • Details of the interim analysis were written in the IDMC RAP.

2.4. Statistical Hypotheses

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

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

The primary objective of the statistical analysis will be to test the null hypothesis in intent-to-treat (ITT) Population that there is no difference between retosiban and atosiban and the alternative hypothesis that there is a difference for the primary endpoint. The hypotheses will be tested at 5% level in a 2-sided test.

3. PLANNED ANALYSES

All planned analyses will be done using SAS version 9.2 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 atosiban) 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 atosiban) 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

5.1.1. Efficacy Analyses

The comparison of the treatment groups for the primary and selected secondary efficacy endpoints (i.e., prolongation of pregnancy, neonatal composite) will be analyzed by the following subgroups if applicable:

- GA at randomization with 4 categories: 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 $^{6/7}$
- Established progesterone group with categories “Yes” and “No”

In addition, for the primary efficacy endpoint, there are no per-protocol population defined, so additional subgroup analyses based on major protocol deviations or violation of PTL criteria (inclusion criteria #4) may be performed as appropriate. Also, additional subgroup analysis based on the status of spontaneous onset delivery will be performed.

5.1.2. Safety Analyses

Safety data will be summarized by the following subgroups if applicable:

- GA at randomization with 4 categories: 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 $^{6/7}$

Additional subgroup analyses may be performed as appropriate.

5.2. Multiplicity Adjustment

There will be no multiplicity adjustment sue 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 Primary and Key Secondary 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 4.

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
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		Y
Obstetrical Medication, Magnesium Sulfate and Antenatal Corticosteroids [3]	Y		Y

NOTES:
1. Listing of subjects 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
- Re-treatment
- 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 and plotted. All disposition summaries will be performed using the 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), percentage of women who failed PTL criteria (inclusion criteria #4), 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 GA strata: $24^{0/7}$ to $25^{6/7}$, $26^{0/7}$ to $27^{6/7}$, $28^{0/7}$ to $30^{6/7}$ and $31^{0/7}$ to $33^{6/7}$)
- Established progesterone use
- Region
- 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 is 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

The primary objective of the statistical analysis will be to test the null hypothesis in the ITT Populations that there is no difference between retosiban and atosiban in time to delivery versus the alternative hypothesis that there is a difference.

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 [1]	Y		Y	Y	Y		Y
Time to delivery, retreatment or subsequent preterm labor) [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, with the exception of individual listings.

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

Primary Statistical Analysis

Endpoint

- Time to delivery (days in 1 decimal point) from the start of IP administration until delivery

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).

Model Specification

- The primary endpoint of time to delivery will be statistically analyzed using a two-component finite mixture regression model. Time to delivery (*y*) is assumed to follow a mixture of two-components with normal densities. Within each component, the expected time to delivery will be modeled as a function of treatment (TRT) as fixed effect, and GA at randomization (GA) and established progesterone use (EP) as covariates.,

$$f(y) = \sum_{k=1}^{2} \pi_k(\alpha, \alpha_k)\, N(\mu_k, \sigma_k^2),$$

where *k* = 2 to denote the 2 groups of mothers namely those who deliver preterm and those who deliver at term.

The component normal distributions depend on the regressors: TRT, GA and EP thru the means μ_k, i.e.,

$$\mu_k = \beta_{0k} + \beta_{1k} \cdot trt + \beta_{2k} \cdot GA + \beta_{3k} \cdot EP,\ \pi_k(trt, GA, EP, \alpha) > 0\ \ \forall k, \sum_{k=1}^{2} \pi_k(trt, GA,\ EP, \alpha) = 1$$

The mixing probabilities π_k, which are non-negative and sum to one, are modeled using a logistic regression model with TRT, GA and EP and corresponding parameters, α, i.e,

$$\pi_1(trt, GA, EP, \alpha) = \frac{\exp(\alpha_0 + \alpha_1 \cdot trt + \alpha_2 \cdot GA + \alpha_3 \cdot EP)}{1 + \exp(\alpha_0 + \alpha_1 \cdot trt + \alpha_2 \cdot GA + \alpha_3 \cdot EP)}$$

$$\pi_2(trt, GA, EP, \alpha) = 1 - \pi_1(trt, GA, EP, \alpha)$$

The patient assignment of each component is determined by the mixture model described

Primary Statistical Analysis

above and some patients are pre-assigned to each component to stabilize the model, i.e. the first component includes those deliveries within 1 week of GA at randomization and the second component includes the patients who deliver after 38 weeks of GA.

The model parameters can then be estimated using PROC FMM from SAS 9.4 by maximizing the likelihood. Point estimate, associated 95% confidence intervals and p-values for the overall average difference between Retosiban and Atosiban is then derived using weighted average of model parameter estimates and variance from each sub-population of mixture model.

- Additionally, treatment by GA at randomization interaction and treatment by progesterone use interaction will also be investigated.

- Terms fitted in the FMM model will include:

Fixed Categorical:	TRT, EP and their interaction term (TRT*EP). Interaction will be included only if the interaction is statistically significant (at 0.05 level of significance).
Fixed Continuous Covariates:	GA and interaction term (TRT*GA). Interaction will be included only if both interaction are statistically significant (at 0.05 level of significance).
Repeated:	None

SAS Code

```
proc fmm data=xxx TECHNIQUE=xxx. partial=xxx ;
 class TRT EP;
 model T2D =  TRT EP GA TRT*GA TRT*EP/ k=2;
 probmodel TRT EP GA TRT*GA TRT*EP;
run;
```

Model Checking & Diagnostics

- Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- Point estimates of the treatment means and standard deviation will be presented, together with the estimate of the treatment mean differences (retosiban – atosiban), the corresponding 95% confidence intervals and p-value.

Summary Results Presentation

- The following plot of the time to delivery per treatment will be generated.
  - Kaplan-Meier Plot of Time to Delivery
- Observed values using descriptive statistics will be presented for each treatment group.
- In addition, time to delivery or retreatment/subsequent preterm labor will be summarized using descriptive statistics.

Primary Statistical Analysis
Sensitivity and Support Statistical Analysis
• Time to delivery will be analyzed using an analysis of covariance adjusting for the covariate of GA at randomization and established progesterone use (yes or no). Additionally, interactions between GA at randomization and treatment and established progesterone use and treatment will also be investigated. • Observed values using descriptive statistics will be presented within defined subgroups in Section 5.1.

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
Key Secondary Endpoints							
Proportion of births prior to $37^{0/7}$ weeks' gestation – ascertain the GA at delivery based on a records review	Y			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			Y			
Length of neonatal hospital stay – duration (in days) of neonatal hospital admission from the medical records	Y			Y			Y
Neonatal composite endpoint	Y			Y			Y
Other Secondary Endpoints							
Individual neonatal composite endpoint				Y			Y
Neonatal composite endpoint without RDS	Y			Y			Y
Neonatal composite endpoint without RDS and mortality	Y			Y			Y
Neonatal admission to a specialized				Y			Y

	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
care unit and length of stay							
Newborn hospital readmission and length of stay				Y			Y
Proportion of births prior to $28^{0/7}$ weeks' gestation	Y			Y			
Proportion of births prior to $32^{0/7}$ weeks' gestation	Y			Y			
Proportion of births prior to $35^{0/7}$ weeks' gestation	Y			Y			
Proportion of births ≤7 days of IP administration	Y			Y			
Proportion of births ≤48 hours of IP administration	Y			Y			
Proportion of births ≤24 hours of IP administration	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. 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

Key Secondary Efficacy Statistical Analysis
Endpoint
• Proportion of births prior to $37^{0/7}$ weeks' gestation • Proportion of births at term (≥ $37^{0/7}$ weeks' gestation) • Length of neonatal hospital stay • Proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite determined up to 28 days after EDD (of $40^{0/7}$ weeks) (details for each composite are provided in Section 11.5.4.) To preserve the overall type I error rate, the key secondary analysis will be performed if and only if the null hypothesis of the primary endpoint is rejected. In addition, a sequential testing method will be used to adjust for multiplicity of the key secondary endpoints such that the type I error rate will be maintained at 5%. The sequential testing examines the hypothesis testing in a pre-specified order, i.e., the testing of the second secondary endpoint will be performed only if the first secondary endpoint is significant at 5%, and testing of the third secondary endpoint will be performed only if the first and second endpoints are significant at 5%. Order of sequential testing is 1) Length of neonatal hospital stay 2) Proportion of births prior to $37^{0/7}$ weeks' gestation and Proportion of births at term 3) Neonate composite outcome
Model Specification
• For the endpoints of neonatal composite outcome, proportion of births prior to $37^{0/7}$ weeks' gestation, and proportion of births at term ($37^{0/7}$ to $41^{6/7}$ weeks' gestation), a logistic regression model will be used for comparing retosiban with atosiban, with GA at randomization and established progesterone use (yes or no) as covariates. The model will use a logit link function to estimate the log odds of percentage of preterm birth. The model will include terms for treatment group, established progesterone use, and GA at randomization. Additionally, interactions between GA at randomization and treatment and established progesterone use and treatment will also be investigated. • Length of hospital stay will be log-transformed (at base 10) prior to analysis. Log-transformed length of hospital stay will be analyzed using an analysis of covariance adjusting for the covariate of GA at randomization and established progesterone use (yes or no). Additionally, interactions between GA at randomization and treatment and established progesterone use and treatment will also be investigated. Wilcoxon rank sum test will also be performed to compare the two treatments if length of hospital stay is not log normal. • Terms fitted in the model will include: Fixed Categorical: TRT, EP and their interaction term (TRT*EP). Interaction will

Key Secondary Efficacy Statistical Analysis	
	be included only if the interaction is statistically significant (at 0.1 level of significance).
Fixed Continuous Covariates:	GA and interaction term (TRT*GA). Interaction will be included only if the interaction is statistically significant (at 0.1 level of significance).
Repeated:	None

SAS Code

- Analysis of Covariance:

```
ods output lsmeans=means diffs=diffs tests3=tests;
proc mixed data=xxx;
    class EP TRT;
    model log_LoS= TRT EP GA TRT*EP TRT*GA/ddfm=kr s;
    lsmeans TRT /pdiff cl alpha=0.05;
run;
```

- Wilcoxon rand sum test:

```
proc npar1way data=xxx Wilcoxon;
     class TRT;
     var log_LoS;
     ods output wilcoxontest=wtest;

run;
```

Model Checking & Diagnostics

- Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- For binary endpoints, the number and percentage of subjects in each treatment group, the relative risk (RR) and 95% CIs, the odds ratio (OR) of response rates (retosiban versus atosiban) and 95% CIs, and p-value will be presented.
- The model-adjusted length of stay will be presented for each treatment group. In addition, the treatment difference between retosiban and atosiban and associated 95% CIs and p-values will be presented.
- Observed values using descriptive statistics for length of stay will be presented for each treatment group.
- For proportion of neonates with any of the composite component, neonates with any of the composite component w/o RDS, neonates with any of the composite component w/o RDS and mortality, and individual composite component, RR and 95% CIs, OR and 95% CIs, and p-values will be provided.

Sensitivity and Support Statistical Analysis

- For length of stay, data will be analyzed in a similar fashion as described in Section 7.1.2.

Key Secondary Efficacy Statistical Analysis
• Treatment effects within defined subgroups in Section 5.1 will be explored.

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. • Neonatal admission to a specialized care unit and length of stay – confirm admission to neonatal intensive or specialized care unit from the medical records • Newborn hospital readmission and length of stay – confirm any neonatal hospital readmission following the birth hospitalization, the reason for admission, and the length of stay from the medical records • Ambulatory surgery – confirm any neonatal ambulatory surgery and the indication for surgery from the medical records • Proportion of births prior to $28^{0/7}$ weeks' gestation • Proportion of births prior to $32^{0/7}$ weeks' gestation • Proportion of births 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
Model Specification
• Binary endpoints will be analyzed in a similar fashion to the neonatal composite analysis in Section 8.1.2. • Neonatal admission to a specialized care unit and length of stay, and ambulatory surgery will be explored in the integrated analysis separately.
Model Results Presentation
• Data will be analyzed in a similar fashion as described in Section 8.1.2. • Treatment effects within defined subgroups in Section 5.1 will be explored.

8.2. Safety Analyses

All safety summaries will be performed for the Safety Population as defined in Section 4 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 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				
AEs by Maximum Grade or Intensity	Y			Y				
Most Common AEs	Y			Y				
Serious AEs	Y			Y				
AEs of special interest	Y			Y				
Disease-related AEs	Y			Y				
AEs leading to Deaths				Y				
Clinical Laboratory	Y			Y	Y			Y
Maternal Vital Signs	Y			Y	Y			Y
Maternal Health Care Resource Use	Y			Y				
Fetal Endpoints								
Adverse Events								
All AEs	Y			Y				
AEs by Maximum Grade or Intensity	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				
AEs by Maximum Grade or Intensity	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			Y				
Neonatal Birth Record	Y			Y				

Endpoints	Observed				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
APGAR scores	Y			Y				
Any Complications				Y				

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- 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, retreatment and total.

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 DBL.

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. Also, the above summary will be produced by subgroups defined in Section **Error! Reference source not found.**.

The AE will be summarized by maternal, fetal and neonatal events, separately. Also, the maternal AE by treatment phase (on-treatment, post-treatment) defined in Section 11.3.3 will be summarized.

8.2.3.2. Adverse Events by Maximum Grade or Intensity

A summary of AEs by grade or intensity will be presented in a table. The grade or intensity that will be presented represents the most extreme grade or intensity captured on the CRF page. The possible grades or intensities are “Not applicable”, “Mild or Grade 1”, “Moderate or Grade 2”, “Severe or Grade 3” and “Grade 4”. In the grade or intensity table, if a patient reported multiple occurrences of the same AE, only the most severe will be presented. AEs that are missing grade or intensity will be presented in tables as “Grade 4” but will be presented in the data listing with a missing grade or intensity.

The AE will be summarized 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 atosiban 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. Also, the above summary will be produced by subgroups as defined in Section **Error! Reference source not found.**.

The SAEs will be summarized by maternal, fetal and neonatal events, separately. Also, the maternal SAEs by treatment phase (on-treatment, post-treatment) defined in Section 11.3.3 will be summarized.

8.2.3.5. Adverse Events Leading to Treatment Discontinuation

A listing of all AEs leading to permanent discontinuation of study drug and/or withdrawal from the study will be produced if applicable.

The AEs leading to permanent discontinuation will be summarized only for maternal events if applicable.

8.2.3.6. 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. Also, the above summary will be produced by subgroups defined in Section **Error! Reference source not found.**.

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

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

8.2.3.7. 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. Also, the above summary will be produced by subgroups defined in Section **Error! Reference source not found.**.

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

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 6.3.7.2 applies

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

8.2.3.8. Death

Deaths will be reported in the similar manner as all AEs. If applicable, a listing of death will be provided by maternal, fetal or 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 length of Intensive Care Unit (ICU) or Neonatal Intensive Care Unit (NICU) in days for neonates at birth by treatment.

The following variables will be summarized with number and percentage for neonates with hospital unit utilization at birth by treatment:

- Total number of neonates with hospital unit utilization at birth
- Hospital unit type (Accident and emergency (observation), General ward, High dependency unit/step down unit, Intensive care unit, etc.)
- ICU or NICU admissions (yes, no)
- Number of ICU or NICU admissions (1, 2, 3, >3)
- Length of hospital stay in days (<=3, > 3-<=7, >7).

RR and 95% CI, OR and 95% CI, and corresponding p-value for ICU or NICU admissions will be provided. ICU or NICU admissions will be analyzed in a similar fashion to the neonatal composite analysis in Section 8.1.2.

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

Maternal health care will be summarized using Maternal Safety Population.

Descriptive statistics will be summarized for cumulative length of hospital stays in days for pre-term labor related hospital admission and hospital admission at delivery by delivery status (Pre-Term Delivery (<37 Weeks of GA), Term Delivery >=37 Weeks of GA)) by treatment. The following variables will be summarized with number and percentage for pre-term labor related hospital admission by treatment:

- Total number of subjects with pre-term labor related hospital admission
- Number of hospital admissions (1, 2, 3, >3)
- Cumulative length of hospital stay in days (<=3, >3-<=7, >7)
- Hospital unit type (Accident and emergency (observation), General ward, High dependency unit/step down unit, Intensive care unit, etc.).

The following variables will be summarized with number and percentage for hospital admission at delivery by delivery status (Pre-Term Delivery (<37 Weeks of GA), Term Delivery >=37 Weeks of GA)) by treatment:

- Number of subjects with hospital admission at delivery;
- Cumulative length of hospital stay in days (<=3, >3-<=7, >7);
- Maternal hospital unit type (Accident and emergency (observation), General ward, High dependency unit/step down unit, Intensive care unit, etc.).

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 outside the reference ranges will be summarized by treatment groups (hematology).

The subjects with laboratory values outside the reference ranges (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.

8.2.8. Placental Data

Placental data including chronic chorio, acute chorio, acute vasculitis, acute funisitis, remote infarction, recent infarction, post mature, intervillous thromb, villous infarctions, chronic villitis, acute villitis, inflammation, meconium will be summarized by treatment group. Also, the summary by GA category at randomization and time from start of IP until delivery will be presented.

All placental 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 following subgroup analyses for the primary and key secondary endpoints will not be performed.
  - Magnesium sulfate use
  - Putative tocolytic use following IP discontinuation
- 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.

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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 Primary and Key Secondary Endpoints with Missing Data • Time to Delivery • Neonatal Composite Outcome • Proportional of Preterm Birth <37 weeks or ≥ 37 weeks • Length of Hospital Stay • **Error! Reference source not found.**
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		Retreatment[1]	Post-Infusion Assessment Phase[2]		Delivery Phase	Maternal Post-Delivery Assessment Phase (via Telephone)	Neonatal Medical Review Phase	Withdrawal From Study
	Day 0	Day 1	Day 2	(Optional – 1 time only)	Face-to-face post-infusion visit	Weekly post-infusion telephone call	Information collected via medical records review	6 weeks after delivery[3]	Delivery to 28 days post EDD	
Clinical and Other Assessments										
Written informed consent and medical releases for treatment[4]	X									
Discuss and request consent for participation in the infant follow-up study[5]		X[5] ◄							► X	X
Inclusion/exclusion criteria confirmation	X			X						
Subject demography	X									
Medical history (including obstetrics history)[6]	X				X		X	X		
Physical examination (including height and weight)	X									
Cervical examination[7]	X	X	X	X	X					
Estimated fetal weight and head circumference via ultrasound[8]	X			X						

Procedures	**Screening Phase**	**Inpatient Randomized Treatment Phase**		**Retreatment[1]**	**Post-Infusion Assessment Phase[2]**		**Delivery Phase**	**Maternal Post-Delivery Assessment Phase (via Telephone)**	**Neonatal Medical Review Phase**	**Withdrawal From Study**
	Day 0	**Day 1**	**Day 2**	**(Optional – 1 time only)**	**Face-to-face post-infusion visit**	**Weekly post-infusion telephone call**	**Information collected via medical records review**	**6 weeks after delivery[3]**	**Delivery to 28 days post EDD**	
Determine AFI via ultrasound[9]	**X**			**X**						
Uterine contractions[10]	**X**									
Schedule face-to-face post-infusion assessment visit			**X**							
Investigational Products[11]										
Investigational product (retosiban or atosiban)		**X**	**X**	**X**						
Efficacy Assessments										
Date and time of delivery							**X**[12]			
Mode of delivery							**X**[12]			
Indication for delivery							**X**[12]			
Neonatal composite outcomes									**X**	
Neonatal hospital stay									**X**	

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

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

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

AE = adverse event; AFI = amniotic fluid index; ALT = alanine aminotransferase; BP = blood pressure; DRE = disease-related event; ECG = electrocardiogram; eCRF = electronic case report form; EDD = estimated date of delivery; EPDS = Edinburgh Postnatal Depression Scale; EQ-5D-5L = EuroQol 5-dimensional 5-level questionnaire; IP = investigational product; LFT = liver function test; PK = pharmacokinetic; SAE = serious adverse event; ULN = upper limit of normal.

1. For undelivered subjects who are subsequently diagnosed with recurrent preterm labor 24 hours or more following completion of the Inpatient Randomized Treatment Phase, retreatment with blinded IP is permitted at the discretion of the investigator (see Protocol Section 3.1.3.1).
2. Subjects who remain undelivered after 48 hours will return for a face-to-face post-infusion assessment visit for obstetric assessments 1 week (acceptable range: 3 to 14 days) following the Inpatient Randomized Treatment Phase. (Note: study documents may reference this visit as the 1-week face-to-face post-infusion assessment visit). The subject will then be contacted every week via telephone to determine if she has delivered or experienced any subsequent episodes of preterm labor. Note: If the subject is scheduled to visit the clinic for reasons not required by this protocol and/or she happens to be present at the time the telephone assessment is due, this assessment may be completed face-to-face. If the subject delivers the baby prior to the face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and LFTs and the assessments for the Delivery Phase (see Protocol Section 3.1.4) will be performed.

3. During the Maternal Post-Delivery Assessment Phase, subjects will be contacted by telephone within 6 weeks of delivery for a post-delivery assessment, including an assessment of AEs (±2 weeks), status of breastfeeding (±2 weeks), and completion of the EPDS (-2 weeks/+6 weeks) and the EQ-5D-5L (-2 weeks/+6 weeks) (see Protocol Section 3.1.5 for list of assessments and visit windows).
4. Prestudy screening information that is collected by the study site may need to come from records that are obtained before the subject has signed the informed consent. The subject will be required to provide written informed consent before any study-specific procedures are performed, and the consent will request permission for use of any information collected prior to its having been signed.
5. The subject or other legal guardian for the infant will be asked to consent to participate in a separate long-term study to follow infants for safety and neurodevelopment outcomes. The subject or other legal guardian for the infant (both delivered and undelivered) will be asked to give consent for the infant follow-up study at any time during the study that is appropriate and convenient. Withdrawal from the study after beginning randomized treatment or discontinuing IP does not preclude involvement in the infant follow-up study.
6. Medical history will be collected at Screening. If a condition with a start date predating Day 0 (Screening) is subsequently discovered, the condition should be recorded in the Medical History eCRF. For obstetrics history, the investigator will make every effort to obtain this information either via computer records, directly from the subject's primary care obstetrician, or via telephone. However, in cases in which these records are not readily available (e.g., off hours, holiday), it is within the investigator's discretion to use gestational age based on the verbal history from the subject with the intent of getting confirmation from the medical records as soon as possible.
7. A cervical examination (including dilation, effacement, and station) will occur at Screening, and an additional cervical examination may be performed before dosing based on investigator discretion. Additional cervical examinations (Day 1, Day 2, and/or at the face-to-face post-infusion assessment visit) are not required but may be performed based on investigator discretion. If inclusion criteria are based on cervical change (see Protocol Section 4.2), 2 examinations must be documented (either 2 digital cervical examinations or 2 cervical length examinations).
8. An ultrasound for estimation of fetal weight and head circumference is needed at Screening or before retreatment unless the date of the most recent ultrasound that includes fetal weight and head circumference is within 3 weeks (21 days) of the date of randomization or the date of retreatment.
9. The abdominal ultrasound for determination of the AFI will be performed at Screening and before retreatment. The AFI should be measured using the 4-quadrant method.
10. Uterine tocography or manual palpation (if necessary) will be performed at Screening. Manual palpations will be permitted if there are technical challenges with measuring contraction frequency.
11. Antenatal corticosteroid treatment should be administered in accordance with national, society, or institutional guidelines. Magnesium sulfate for fetal neuroprotection can be given at the discretion of the investigator.
12. Information regarding delivery will be obtained through a review of the hospital and medical records. Growth parameters include neonatal weight, length, and head circumference.
13. A 12-lead ECG will be performed prior to dosing. If the results are interpreted by the investigator to have clinically significant abnormalities, the subject cannot be dosed.
14. Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) will be assessed at Screening, as part of maternal safety monitoring during the Inpatient Randomized Treatment Phase and, if criteria are met, also during retreatment, and at the post-infusion assessment visit. During the Inpatient Randomized Treatment Phase and during retreatment, vital signs will be assessed and recorded within the following windows relative to the start of the infusion: 15 to 30 minutes, 4 to 8 hours, and 20 to 24 hours, at the end of the infusion, at the time of any dose changes, and as warranted by a medical condition. It is suggested (<u>but not required</u>) that oxygen saturation also be assessed at Screening and recorded in source documents.
15. Maternal subjects will complete the EPDS, a self-reported questionnaire, at the maternal follow-up assessment 6 weeks (-2 weeks/+6 weeks) after delivery.
16. The LFTs should be ordered from the local laboratory before dosing with the IP. If the local laboratory results are available before the start of dosing, confirm that ALT is not ≥2 × ULN OR total bilirubin is not >1.5 × ULN (>35% direct bilirubin). An isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%. Screening LFT laboratory results do not need to be available for the subject to be randomly assigned to treatment or for the start of dosing with IP; however, see Protocol Section 6.3.1 if ALT or bilirubin is abnormal.

17. Hematology, chemistry, and LFTs will be determined through a central laboratory at the screening, Day 2, and the face-to-face post-infusion assessment visits. The LFT values from the central laboratory should be reviewed for abnormalities (see Protocol Section 6.3.1). For subjects who deliver within 24 hours after completion or discontinuation of IP and for subjects who deliver at the investigative center after discharge but before the face-to-face post-infusion assessment visit, central laboratory assessments for hematology, chemistry, and LFTs should be performed. For subjects that do not deliver at the investigative center, central laboratory assessments for hematology, chemistry, and LFTs should be performed at the investigative center within 1 week (acceptable range: 3 to 14 days) after completion of the study drug infusion.
18. Prior to dosing, if the fetal heart rate pattern is nonreassuring, the subject cannot be dosed.
19. Electronic fetal monitoring is required for a minimum of 6 hours from the start of the infusion or from the start of a dose increase. As long as the fetal heart rate pattern is consistently reassuring throughout the required 6-hour duration of monitoring and the contraction frequency is ≤2 in a 30-minute window within the last hour of monitoring, continuous monitoring may be discontinued and nonstress tests initiated at a minimum of every 8 hours and as needed. Electronic fetal monitoring, including the fetal heart rate and fetal heart rate category, will be recorded in the eCRF with maternal vital signs. Any fetal heart rate assessment of Category II or III will be reported as an AE of special interest on a specified eCRF (details in Protocol Section 6.3.12.3**Error! Reference source not found.**).
20. If the subject has not delivered at the end of the Inpatient Randomized Treatment Phase, fetal heart rate (fetal Doppler heart rate or cardiotocography are both acceptable) will be recorded at the face-to-face post-infusion assessment visit. Any fetal heart rate assessment of Category II or III will be reported as an AE of special interest on a specified eCRF (details in Protocol Section 6.3.12.3).
21. During the Delivery Phase, fetal heart rate just prior to delivery will be collected, if available, from review of delivery records. Any fetal heart rate assessment of Category II or III will be reported as an AE of special interest on a specified eCRF (details in Protocol Section 6.3.12.3).
22. Maternal and neonatal health care resource use may include, but is not limited to, neonatal complications requiring intensive or specialized care, neonatal hospital readmission, and neonatal ambulatory surgery.
23. PK samples will be taken at the following sampling windows (relative to the start of the infusion): 2 to 4 hours, 10 to 14 hours, 22 to 26 hours, and 48 to 54 hours. In addition, a PK sample should be taken at the onset of any maternal or fetal SAE that occurs within 12 hours after completion or discontinuation of IP. A maternal blood sample should be collected at the same time as the cord blood sample (see Protocol Section 6.5.1) if the sample time does not already coincide with one of the PK sampling windows.
24. In subjects who deliver at an investigative center within 12 hours following completion or discontinuation of the IP, the cord blood sample will also be divided for PK analysis as well as genetic (if additional consent is provided; Protocol Appendix 1) and biomarker analyses.
25. A breast milk/colostrum sample is only to be collected in women who deliver and produce breast milk within 12 hours after completion or discontinuation of the IP.
26. A placental tissue sample will be collected at delivery in subjects who deliver at an investigative center.
27. A maternal blood sample for genetic research will only be collected from subjects who provide separate informed consent (see Protocol Appendix 1).
28. A cord blood sample will be collected in subjects who deliver at an investigative center, if additional consent is provided.
29. Testing for fetal fibronectin will be performed only at those institutions collecting the information as routine practice. Fetal fibronectin will not be used to determine study eligibility.
30. Cervical length measured by transvaginal ultrasound will be captured only at those institutions collecting the information as routine practice. Cervical length will not be used to determine study eligibility.

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. For retreated subjects, start date/time and stop date/time for both initial treatment and retreatment will be derived.

11.3.1. Treatment Phases

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

Non-retreated subjects

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

Retreated subjects

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

Non-retreated subjects

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.

Retreated subjects

Treatment State	Definition
AE = Pre-treatment	AE Start Date < Initial 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. Initial Study Treatment Start Date ≤ AE Start Date ≤ Initial Study Treatment Stop Date + 1 or Retreated Study Treatment Start Date ≤ AE Start Date ≤ Retreated Study Treatment Stop Date + 1
AE = Post-treatment	If AE onset date is after the treatment stop date. Initial Study Treatment Stop Date + 1 < AE Start Date < Retreated Study Treatment Start Date or AE Start Date > Retreated Study Treatment Stop Date + 1
AE Onset Time Since 1st Dose (Days)	If Initial Study Treatment Start Date > AE Onset Date : **= AE Onset Date – Initial Study Treatment Start Date** If Initial Study Treatment Start Date ≤ AE Onset Date : **= AE Onset Date – Initial Study Treatment Start Date + 1** Missing otherwise

Treatment State	Definition
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	Atosiban	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. For the retreated subjects, a baseline will be the latest pre-dose assessment of the initial treatment.

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 assessments 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 interruptions 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

- 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 retreatment/subsequent preterm labor is defined as the days between start time of the infusion of IP and the first occurrence among delivery, retreatment and subsequent preterm labor 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

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>Partial dates will be displayed as captured in subject listing displays.</td></tr>
<tr><td>Concomitant Medication</td><td>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.</td></tr>
<tr><td>Time to Delivery</td><td>For the delivery date/time of the primary endpoint,
Missing data with respect to time to delivery endpoint 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.</td></tr>
<tr><td>Adverse Events (General)</td><td>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</td></tr>
<tr><td>Adverse Events (Mother)</td><td>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 :
<table>
<tr><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.
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.
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).</td></tr>
<tr><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.</td></tr>
</table></td></tr>
</table>

Element	Reporting Detail	
		○ 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. ○ 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.
Adverse Events (Neonate)	• 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:	
	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. • 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).
	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. • 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.
Adverse Events (Fetus)	• 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:	
	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. • 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 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'

Element	Reporting Detail		
			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 Primary and Key Secondary Endpoints with Missing Data

11.7.1. Time to Delivery

The time to delivery is defined as the days between the delivery and start time of the infusion of IP. If the delivery date is missing or unknown i.e. subjects withdrew from the study or lost to follow-up, the time to delivery data will be the missing data, which will be handled in below methods.

This analysis addresses the question "What is the prolongation effect for the mother of an initial decision to prescribe treatment, regardless of what subjects received?" This is also referred to as a *de facto* analysis (Carpenter 2013). The treatment effect on the time to delivery will be estimated on randomized subjects regardless of adherence. The delivery data after treatment discontinuation, treatment switch (i.e. at retreatment), or use of rescue medication will be collected and will be included in the primary analysis. Missing data from subjects who withdraw from study participation will be imputed using last contact date or last record available in the study database. The last record are those clinical records that the subjects were last contacted but remained undelivered. For those subjects who are lost to follow-up, a date of birth of delivery date will be obtained from the search of national database if applicable.

11.7.2. Neonatal Composite Outcome

Neonatal Composite outcome is proportion of neonates with any diagnosis from the neonatal morbidity and mortality composite determined up to 28 days after EDD (of $40^{0/7}$ weeks).

This analysis is also a *de facto* analysis as defined for time to delivery, and will include all mother and neonate pairs regardless of adherence. The delivery data after treatment discontinuation, treatment switch (i.e. at retreatment), or use of rescue medication will be collected and will be included in the primary analysis.

Analysis of the primary endpoint will be performed using multiple imputation methods described as below (Carpenter et al 2013). The MI method will be implemented with the SAS® MI procedure, using the logistic regression method. The model includes treatment (TRT) and GA at birth (GA_birth) as predictors, where GA at birth is considered complete with missing values (if any) being imputed with the last contact date or last record available. PROC MI will replace each missing neonatal composite score with a set of plausible values, assuming data are MAR. The missing data will be filled in 1000 times to generate 1000 complete data sets. Sample SAS® code of the procedure can be found in below:

```
proc mi data=dsetin seed=xxx out=dsetmi nimpute=1000;
     class TRT composite;
     monotone logistic;
     var TRT GA_birth composite;
run;
```

Once the 1000 completed datasets are produced, analysis of the neonatal composite outcome will be repeated on these imputed datasets, using a logistic regression model to estimate the effect of treatment on the outcome adjusting for GA at randomization(GA_rand) and progesterone use as covariate:

```
proc logistic data=dsetmi;
      class TRT(desc);
      model composite(event='1') = TRT GA_rand EPU;
      ods output PARAMETERESTIMATES=parms ODDSRATIOS=odds;
      by _Imputation_;
run;
```

PROC MIANALYZE will then be used to combine the results of analyses on the multiply imputed datasets based on Rubin's combination rules (Rubin, 1987).

As the estimates of odds ratios follow a log-normal distribution, a log transformation can be applied to normalize these estimates in order to be able to apply Rubin's rules. These combination rules take as input estimates of a statistic obtained from multiple imputed datasets as well as standard errors of these estimates, and produce the overall pooled estimate, overall standard error, confidence interval and a p-value from a univariate hypothesis test of the statistic being equal to zero. An example of SAS® code is given below:

```
*** log-transform odds ratio estimates and obtain standard error from CIs;

data lgodds;
      set odds(where=(index(effect,"TRT")));
      log_or=log(OddsRatioEst);
      log_or_se=(log(UpperCL)-log(LowerCL))/(2*1.96);
run;

*** combine transformed estimates;

proc mianalyze data=lgodds;
      modeleffects log_or;
      stderr log_or_se;
      ods output PARAMETERESTIMATES=lgsodds_mi;
run;

*** back-transform combined values;

data odds_mi;
      set lgsodds_mi;
      OddsRatioEst = exp(estimate); * pooled odds ratio;
      LowerCL=OddsRatioEst*exp(-1.96*stderr); * pooled lower limit;
      UpperCL=OddsRatioEst*exp( 1.96*stderr); * pooled upper limit;
run;
```

11.7.3. Proportional of Preterm Birth <37 weeks or ≥ 37 weeks

If the delivery date is missing or unknown i.e. subjects withdrew from the study or lost to follow-up, the proportion of births data will be the missing data, which will be handled in below methods.

The analysis of proportion of preterm birth uses the *de facto* analysis. Missing data from subjects who withdraw from study participation will be imputed using last contact date or last record available in the study database. The last record are those clinical records that the subjects were last contacted but remained undelivered.

11.7.4. Length of Hospital Stay

The handling of missing data in neonatal hospital length of stay can be summarized as follows.

Length of hospital stay will be log-transformed (at base 10) and checked for normality prior to analysis. If the normality assumption holds, the missing values in the length of hospital stay will be multiple imputed and then analyzed using an analysis of covariance adjusting for the covariate of GA at entry and established progesterone use (yes or no). If the normality assumption is violated, the missing values will not be imputed and Wilcoxon rank sum test will be performed to compare the two treatments with all observed data.

If the length of stay data is log-normally distributed, the missing data (in log scale) will be imputed using the SAS® MI procedure with the regression method. The model includes treatment (TRT) and GA at birth (GA_birth) as predictors, where GA at birth is considered complete with missing values (if any) being imputed with the last contact date or last record available in the study database. The missing data will be filled in 1000 times to generate 1000 complete data sets. Sample SAS® code of the procedure can be found in below:

```
proc mi data=dsetin seed=xxx out=dsetmi nimpute=1000;
     class TRT;
     monotone regression;
     var TRT GA_birth log_length_stay;
run;
```

Once the 1000 completed datasets are produced, analysis of the log-transformed length of hospital stay will be repeated on these imputed datasets, using a regression model to estimate the effect of treatment adjusting for GA at randomization (GA_rand) as continuous covariate and established progesterone use (EPU) as categorical covariate:

```
proc mixed DATA=dsetmi;
     class TRT EPU ;
     model log_length_stay = TRT GA_rand EPU / solution cl;
     lsmeans trtmt / cl diff;
     by _Imputation_;
```

```
    ods output diffs=lgdiffs SolutionF=params CovB=covb;
run;
```

PROC MIANALYZE will then be used to combine the results of analyses on the multiply imputed datasets based on Rubin's combination rules (Rubin, 1987):

```
proc mianalyze data=lgdiffs;
    modeleffects estimate;
    stderr stderr;
    ods otuput PARAMETERESTIMATES=diffs_mi;
run;
```

The combined results will be back transformed to normal scale afterwards.

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)	• Time to delivery • Length of hospital stay
Analysis	• Finite Mixture Models for the Time to Delivery • Analysis of Covariance for the Length of hospital stay

- For the time to delivery, the FMM model assumptions will be examined and appropriate adjustments maybe applied based on the data.
- 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	Amniotic 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
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee

Abbreviation	Description
IDSL	Integrated Data Standards Library
IP	Investigational Product
ITT	Intent-to-treat
Kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
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

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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	Figures
Study Population	1.01 to 1.xx	1.01
Efficacy	2.01 to 2.xx	2.01
Safety	3.01 to 3.xx	N/A
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		
1.27	Maternal ITT		Summary of Maternal Prior Medications		
1.28	Maternal ITT		Summary of Maternal Concomitant Medications		
1.29	Maternal ITT		Summary of Maternal Obstetrical Medications		

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
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		Analysis of Time to Delivery		
2.03	Maternal ITT		Summary of Time to Delivery, Retreatment or Subsequent PTL		
2.04	Maternal ITT		Analysis of Time to Delivery Using ANCOVA		
2.51	Maternal ITT		Summary Statistics for Time to Delivery by Gestational Age Group		
2.52	Maternal ITT		Summary Statistics for Time to Delivery by Established Progesterone Group		
2.53	Maternal ITT		Summary Statistics for Time to Delivery by PTL criteria (IC#4)		
2.54	Maternal ITT		Summary Statistics for Time to Delivery by Labor Onset Status		
Neonatal Composite Endpoint					
2.101	Neonatal ITT		Proportion of Neonatal Composite Endpoint		
2.102	Neonatal ITT		Proportion of Modified Neonatal Composite Endpoint		
2.151	Neonatal ITT		Proportion of Neonatal Composite Endpoint by Gestational Age Group		

Efficacy Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.152	Neonatal ITT		Proportion of Neonatal Composite Endpoint by Established Progesterone Group		
Proportion of Births					
2.181	Maternal ITT		Proportion of Births		
2.201	Maternal ITT		Proportion of Births by Gestational Age Group		
2.202	Maternal ITT		Proportion of Births by Established Progesterone Group		
Neonatal Hospital Admission: Length of Neonatal Hospital Stay					
2.301	Neonatal ITT		Analysis of Neonatal Hospital Stay		
2.321	Neonatal ITT		Summary Statistics for Neonatal Hospital Stay by Maternal Gestational Age Group		
2.322	Neonatal ITT		Summary Statistics for Neonatal Hospital Stay by Established Progesterone Group		

11.11.4. Efficacy Figures

Efficacy Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Time to Delivery					
2.01	Maternal ITT		Kaplan-Meier Plot of Time to Delivery by Treatment Group		

11.11.5. 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		
3.31	Maternal Safety		Summary of Maternal Adverse Events by Maximum Grade or Intensity		
3.41	Maternal Safety		Summary of Most Common Maternal Adverse Events		
3.51	Maternal Safety		Summary of Maternal Serious Adverse Events		
3.71	Maternal Safety		Summary of Maternal Adverse Events of Special Interest		
3.72	Maternal Safety		Summary of Maternal Adverse Events of Special Interest by Gestational Age Group		

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.81	Maternal Safety		Summary of Maternal Disease-Related Adverse Events		
Fetal Adverse Events					
3.111	Maternal Safety		Summary of Fetal Adverse Events		
3.131	Maternal Safety		Summary of Fetal Adverse by Maximum Grade or Intensity		
3.141	Maternal Safety		Summary of Most Common Fetal Adverse Events		
3.151	Maternal Safety		Summary of Fetal Serious Adverse Events		
3.171	Maternal Safety		Summary of Fetal Adverse Events of Special Interest		
3.172	Maternal Safety		Summary of Fetal Adverse Events of Special Interest by Gestational Age Group		
Neonatal Adverse Events					
3.211	Neonatal Safety		Summary of Neonatal Adverse Events		
3.231	Neonatal Safety		Summary of Neonatal Adverse by Maximum Grade or Intensity		

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
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		
3.272	Neonatal Safety		Summary of Neonatal Adverse Events of Special Interest by Gestational Age Group		
3.281	Neonatal Safety		Summary of Neonatal Disease-Related Adverse Events		
Maternal Hospital Admission					
3.301	Maternal Safety		Summary of Maternal Hospital Admission (In-patient)		
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		
Neonatal Hospital Admission					
3.463	Neonatal Safety		Summary of Neonatal Hospital Unit Utilization At Birth		
3.464	Neonatal Safety		Analysis of Length of Neonatal NICU Stays At Birth		
Maternal Placental Data					
3.501	Maternal Safety		Summary of Placental Findings		

11.11.6. 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		
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		

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
12	Maternal ITT		Maternal Baseline Characteristics I		
13	Maternal ITT		Maternal Baseline Characteristics II		
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 Safety		Prior and Concomitant Medications		
24	Maternal Safety		Obstetrical Medications		
25	Maternal Safety		Magnesium Sulfate		
26	Neonatal Safety		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		
46	Maternal Safety		Maternal Adverse Events of Special Interest: Pelvic Abscess		
49	Maternal Safety		Maternal Adverse Events of Special Interest: Wound Infection		
52	Maternal Safety		Maternal Adverse Events of Special Interest: Postpartum Hemorrhage		
53	Maternal Safety		Maternal Adverse Events of Special Interest: Placental Abruption		
56	Maternal Safety		Fetal Adverse Events of Special Interest: Category II-III FHR Event		
57	Maternal Safety		Maternal Disease-Related Adverse Events		

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
76	Maternal Safety		All Fetal Adverse Events		
77	Maternal Safety		Fetal Serious Adverse Events		
78	Maternal Safety		Fetal Adverse Events of Special Interest		
82	Neonatal Safety		All Neonatal Adverse Events		
83	Neonatal Safety		Neonatal Serious Adverse Events		
84	Neonatal Safety		Neonatal Adverse Events of Special Interest		
86	Neonatal Safety		Neonatal Adverse Events of Special Interest: Respiratory Distress Syndrome		
89	Neonatal Safety		Neonatal Adverse Events of Special Interest: Intraventricular Hemorrhage		
91	Neonatal Safety		Neonatal Adverse Events of Special Interest: Neonatal Acidosis		
92	Neonatal Safety		Neonatal Adverse Events of Special Interest: Hyperbilirubinemia		

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
96	Neonatal Safety		Neonatal Disease-Related Adverse Events		
97	Neonatal Safety		Neonatal Deaths		
111	Neonatal Safety		Neonatal Disease-Related Adverse Events: Retinopathy of Prematurity		
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		

11.11.7. 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		
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]**
405	Maternal Safety		Cervical Exam		
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		
Placental Data					
464	Maternal Safety		Placental Findings		