Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP) Version 2.0

Title	:	Reporting and Analysis Plan for Follow-Up Study to Assess Long-Term Safety and Outcomes in Infants and Children Born to Mothers Participating in Retosiban Treatment Studies
Compound Number	:	GSK221149
Effective Date	:	5-DEC-2019

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 200722.
- This RAP is intended to describe the planned 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.
- Change in Version 2.0: Change from '<70' to '<4' for cognitive scale score, gross motor scale score and fine motor scale score of >2 SDs below mean score in Section 2.2.

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This Reporting and Analysis Plan (RAP) details all planned safety analyses and outputs required for the final Clinical Study Report (CSR) of study 200722.
Protocol	• This RAP is based on the original protocol (Dated: 14-May-2014), protocol amendment 01 (Dated: 17-Aug-2015), protocol amendment 02 (Dated: 01-Nov-2018) of study GSK200722 [GlaxoSmithKline Document Numbers: 2014N194466_00, GlaxoSmithKline Document Numbers 2014N194466_01, and GlaxoSmithKline Document Numbers 2014N194466_02] and the most recent version of the electronic Case Report Form (eCRF).
Objective	**To assess the safety and outcomes in infants and children who were exposed to retosiban or comparator in the Phase III Spontaneous Preterm Labor (SPTL) treatment studies.**
Endpoint	**Morbidity and mortality endpoints.** **Neurodevelopment endpoints.** **Exploratory resource utilization endpoint.** **Details are further defined in Section 2.2.**
Study Design	**Long-term infant and child follow-up study (with no medical interventions or study visits to an investigational site required), during which parents or legal guardians will complete developmental questionnaires and other data on their children's health status via an electronic device at prespecified intervals until their children reach 24 months corrected age (or chronological age, if applicable), to prospectively assess safety and outcomes of all infants and children born to women who received at least 1 dose of retosiban or comparator in any of the Phase III SPTL treatment studies.**
Planned Analyses	• There is no formal interim analysis planned for this study. • Final 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.
Analysis Population	• The primary population for safety assessment will be the Infant Safety population. • The ARIOS Safety population is a subset of the Infant Safety population for which the mother/infant pairs who enrolled into the ARIOS study
Hypothesis	• The objective of the study is to describe the safety and morbidity and mortality outcomes of children exposed to treatment during Phase III SPTL studies investigating retosiban or comparator for the treatment of SPTL. • No type I error adjustments are planned.

Safety Analyses	• Descriptive statistics will be used to describe the safety and morbidity and mortality outcomes of children exposed to treatment during the Phase III SPTL studies investigating retosiban or comparator for the treatment of SPTL. • Descriptive statistics will be used to describe the clinical safety in terms of neurodevelopment in infants and children exposed to retosiban or comparator. • Serious Adverse Events (AEs) will be summarized by in infants exposed to retosiban or comparator in the Phase III SPTL treatment studies.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Due to early termination of the study, not all originally planned data analyses as outlined in the protocol will be performed. More details are given in Section 8.

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

Objectives	Endpoints

• To characterize the clinical safety in terms of infant and child morbidity and mortality in infants and children exposed to retosiban or comparator in utero	• Proportion of infants and children with newly diagnosed (after 28 days post EDD) chronic medical conditions by type of condition will be recorded and include the following:
	  • Respiratory conditions
	  ○ Chronic lung disease
	  ○ Reactive airway disease
	  ○ Vocal cord paralysis
	  ○ Airway obstruction
	  • Neurological conditions
	  ○ Cerebral palsy
	  ○ Seizure disorder
	  ○ Hydrocephalus requiring shunt
	  • Sensory conditions
	  ○ Vision
	  ○ Vision impairment
	  ○ Blindness in 1 or both eyes, or sees light only
	  ○ Hearing
	  ○ Hearing impairment
	  ○ Deafness in 1 or both ears
	  ○ Hearing impaired, uncorrected even with aids
	  • Gastrointestinal conditions
	  ○ GERD (moderate to severe)
	  ○ Tube/parenteral feeding
	  ○ Short bowel syndrome
	  • Cardiovascular conditions
	  ○ Pulmonary hypertension
	  ○ Hypertension
	  • Renal conditions
	  ○ Renal impairment requiring dialysis
	  • Growth parameters
	  ○ Poor weight gain
	  ○ Reduced length
	  ○ Reduced head circumference
	  ○ Failure to thrive
	• Proportion of infants and children with newly diagnosed (after 28 days post EDD) congenital anomalies
	• Proportion of infant and child deaths that occur after 28 days post EDD and until 24 months chronological age[1]

Objectives	Endpoints

	• Neurodevelopment endpoints assessed at ages 9, 18, and 24 months, corrected for prematurity:
	  • Proportion of infants with an ASQ-3 score in the black zone in any domain
	  • Proportion of infants with an ASQ-3 score in the black zone for gross motor skills
	  • Proportion of infants with an ASQ-3 score in the black zone for fine motor skills
	  • Proportion of infants with an ASQ-3 score in the black zone for communication
	  • Proportion of infants with an ASQ-3 score in the black zone for problem-solving
	  • Proportion of infants with an ASQ-3 score in the black zone for personal-social skills
	  • Proportion of infants referred for developmental evaluation (using BSID-III)
	  • Proportion of infants with a BSID-III score >2 SDs below the mean score for the cognitive scale (<4)
	  • Proportion of infants with BSID-III score >2 SDs below the mean score for the gross motor scale (<4)
	  • Proportion of infants with BSID-III score >2 SDs below the mean score for the fine motor scale (<4)
	  • Proportion of infants with a BSID-III score >2 SDs below the mean score for the language scale (<70)
	  • Proportion of infants with a CBCL/1.5-5 score above the 97th percentile for a subset of prespecified questions that relate to attention and hyperactivity problems
	  • Proportion of infants indicated as needing further evaluation after completion of the M-CHAT-R/F
	  • Proportion of infants referred for neurological evaluation to determine diagnosis of cerebral palsy
	• Proportion of infants with at least 1 of the following indicators of neurodevelopmental impairment:
	  • Hearing impaired, uncorrected even with aids (at 24 months chronological age)
	  • Blindness in 1 or both eyes, or sees light only (at 24 months chronological age)
	  • Cerebral palsy (moderate and severe) (at 24 months corrected age[2])
	  • Cognitive impairment: BSID-III Cognitive Scale Score of >2 SDs below mean score (<4) (at 24 months corrected age)
	  • Motor impairment: BSID-III Motor Composite Scale Score of >2 SDs below mean score (<70) (at 24 months corrected age)
	  • Diagnosis of ASD, ADD, or ADHD

Objectives	Endpoints
Exploratory	
• To characterize parental productivity loss related to a sick child and infant resource utilization in terms of hospital admissions, length of stay, ER/UC visits, surgical procedures, and referral to specialty care or therapy visits for infants (up to age 2 years) exposed to retosiban or comparator in utero	• Number of hospital admissions, proportion of infants and children with any hospital admission, post-birth hospitalization discharge, by principal and secondary discharge diagnosis, type of hospital unit admitted to (e.g., NICU, Pediatric, PICU, Nursery level 3, ICU), and length of hospital stay per unit after 28 days post EDD and until 24 months chronological age • Combined length of hospital stay in days for all hospital admissions (for infants discharged from the delivery hospitalization and for babies who were never discharged home post-delivery) after 28 days post EDD and until 24 months chronological age Number of surgical procedures (details of type and whether performed on an inpatient basis or at an outpatient/surgical center will be collected up to 24 months chronological age only) after 28 days post EDD and until 24 months chronological age Number of ER/UC visits and proportion of infants with any ER/UC visit after 28 days post EDD and up to 24 months chronological age • Number of specialty care or therapy visits and proportion of infants referred for specialty care or therapy by type of care/therapy after 28 days post EDD and up to 24 months chronological age • Parental productivity loss related to infant hospital admissions, ER/UC visits, or specialist care after 28 days post EDD and up to 24 months chronological age

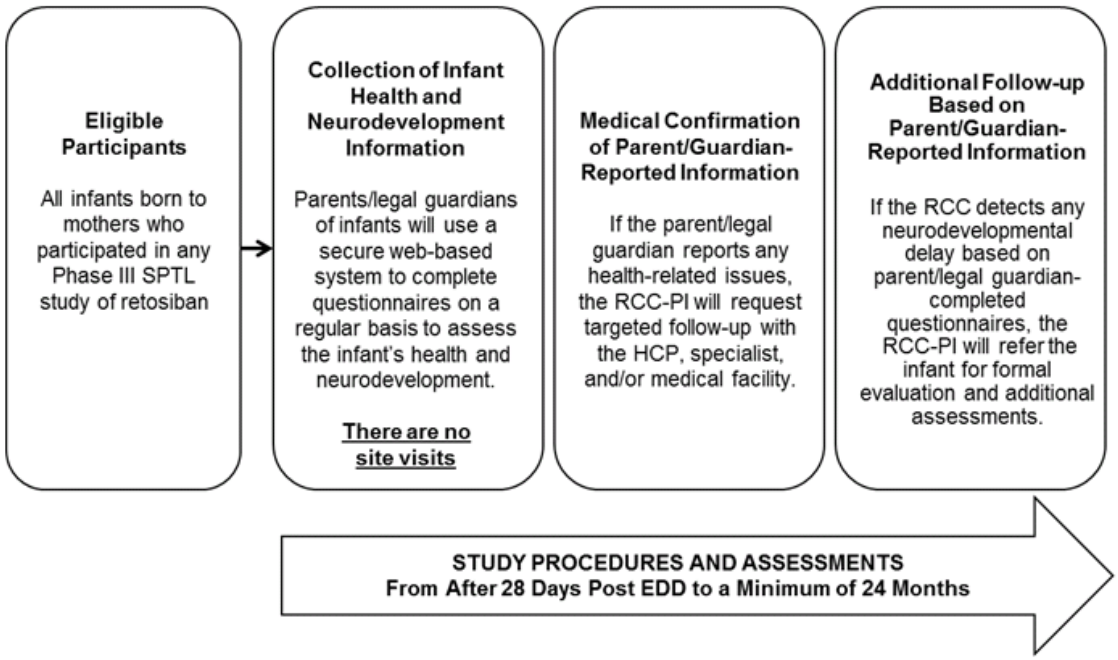
ADD = attention deficit disorder; ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; ASQ-3 = Ages and Stages Questionnaire-3; BSID-III = Bayley Scales of Infant Development, third edition; CBCL/1.5-5 = Child Behavior Checklist for Ages 1.5 to 5; EDD = estimated date of delivery; ER/UC = emergency room/urgent care; GERD = gastroesophageal reflux disease; ICU = intensive care unit; M-CHAT-R/F = Modified Checklist for Autism in Toddlers-Revised with Follow-Up; NICU = neonatal intensive care unit; PICU = pediatric intensive care unit.

[1] Chronological age is age [in months] after the infant was born

[2] Corrected age is age [in months] after expected date of full-term delivery (chronological age minus the number of months that the infant was born early)

2.3. Study Design

Overview of Study Design and Key Features



EDD = estimated date of delivery; HCP = health care provider; RCC = research coordinating center; RCC-PI = research coordinating center-principal investigator; SPTL = spontaneous preterm labor.

Overview of Key Study Design Features	
Design Features:	• Long-term infant and child follow-up study (up to 24 months corrected age (or chronological age, if applicable)) • Subjects are infants and children born to women who received at least 1 dose of retosiban or comparator in any of the Phase III SPTL treatment studies. • This study does not require medical interventions or study visits to an investigational site. • Parents or legal guardians will be prompted at certain time points to complete developmental questionnaires and other data on their children's health status via an electronic device until infants and children have reached 24 months corrected age (or chronological age, if applicable).
Dosing:	• Infants and children enrolled in this study will not be administered any investigational product.
Treatment Assignment:	• The Phase III SPTL treatment study treatment group and strata to which mothers were dosed will be maintained during analysis of data from the child follow-up study.
Interim Analysis	• There is no formal interim analysis planned for this study.

2.4. Statistical Hypotheses

The objective of the study is to describe the safety and morbidity and mortality outcomes of children exposed to treatment during Phase III SPTL studies investigating retosiban or comparator for the treatment of SPTL. These mortality and morbidity endpoints (as described in protocol Section 6.2) will be descriptively summarized.

Protocol amendment 02 has updated the total study duration to 2 years. Babies or infants that have passed the 2-year assessments after the amendment implementation are not required to continue further within the study, nor do they need to complete any subsequent stud- related assessments.

Descriptive summaries will utilize data collected up to and including the 2-year assessments. Data collected beyond the 2 year assessment will be presented, but not included in the summaries.

No type I error adjustments are planned.

3. PLANNED ANALYSES

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

3.1. Interim Analyses

There is no formal interim analysis planned for this study.

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. Actual treatment data have been distributed.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Infant Safety	• All the infants whose mothers have been randomized and received retosiban or comparator in any of the Phase III treatment trials will be included in the Infant Safety analysis population. • Of these mothers, the Infant Safety population includes the mother/infant pairs who enrolled into the ARIOS study, the mother/infant pairs who decline to consent to the study, and the mother/infant pairs whose fetus/neonates/infants has died prior to the enrolment of the study. • Subjects will be analyzed according to their actual treatment in case this differs from their randomized treatment.	• Disposition • All safety analyses
ARIOS Safety	• Subset of the Infant Safety population for which the mother/infant pairs enrolled into the ARIOS study.	• Demographic • All safety analyses

Data collected up to and including the 2-year assessments will be included in the descriptive summaries. Data collected beyond the 2-year assessment will be presented, but not included in the summaries.

4.1. Protocol Deviations

Protocol deviations are tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (Reference).

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Primary Comparisons of Interest

The primary treatment groups are retosiban, placebo, and atosiban.

The primary comparisons between these treatment groups will be:

- Retosiban versus placebo
- Retosiban versus atosiban

5.2. Other Comparisons of Interest

A secondary treatment group will include the pooling of placebo and atosiban into a group called “all comparators”. The secondary comparison will be the following:

- Retosiban versus all comparators

5.3. Multiplicity Adjustment

There will be no multiplicity adjustment.

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
10.1	Appendix 1: Protocol Deviation Definitions
10.2	Appendix 2: Time and Events
10.3	Appendix 3: Treatment States and Phases
10.4	Appendix 4: Data Display Standards & Handling Conventions
10.5	Appendix 5: Derived and Transformed Data
10.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
10.7	Appendix 7: Abbreviations & Trade Marks
10.8	Appendix 8: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Planned Analyses Overview

All analyses will be based on both populations as defined in Section 4, except where specified.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 8: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated		
	Table	Figure	Listing
Subject Disposition (Infant Safety population, only)			
Subject Disposition	Y		Y
Reasons for Withdrawals	Y		Y
Number of Infants Enrolled at Milestone	Y		
Demography (ARIOS Safety population, only)			
Demographics and Baseline Characteristics	Y		Y
Race & Racial Combinations	Y		Y

NOTES:
1. Subject Disposition TLFs will only be created for the Infant Safety population.
2. Demography TLFs will only be created for the ARIOS Safety population
3. Y = Yes display generated

6.2. Disposition of Subjects

Analyses of disposition data will be based only on the Infant Safety population as defined in Section 4.

Subject status with respect to study status will be summarized in relation to:

- Enrolled
- Not enrolled
- Died in treatment studies
- Study completion and withdrawal/death

The number and percentage of subjects with the above study status will be reported by treatment group. Reasons for withdrawal will be presented.

Subject status with respect to each study milestone will be summarized in relation to:

- Treated at treatment studies
- Infant consented to ARIOS
- Infant not consented to ARIOS
- Enrolled at ARIOS

The number and percentage of subjects with the above study milestone will be reported by treatment group. The number and percentage of subjects reaching each study milestone after enrolling in ARIOS (infant death, 9 months, 18 months, and 24 months) will be presented.

A completed subject is defined as one who has completed all phases of the study up to and including the 2-year assessment. Note: due to protocol amendment 02 which updated the total study duration to 2 years, some infants may have data collected after the 2-year assessment.

Subject disposition data will also be listed. All disposition summaries will be performed using the Infant Safety population.

6.3. Demographic and Baseline Characteristics

Analyses of demographic and baseline characteristics will be based only on the ARIOS Safety population as defined in Section 4.

Continuous variables, such as birth weight (kg), APGAR at 5 minutes after birth, and other baseline characteristics as needed will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) by treatment group.

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

- Age of infant at enrollment
- Sex
- Birth weight category (<1 kg, 1 - < 2.5 kg, and >= 2.5 kg)
- Maternal 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 $33^{6/7}$)
- Infant GA at birth (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 $33^{6/7}$, $34^{0/7}$ to $36^{6/7}$, and $37^{0/7}$ to $41^{6/7}$)
- APGAR category at 5 minutes after birth (<7 and >= 7)

Demographic and baseline characteristics data will also be listed. Summaries will be performed using the ARIOS Safety population. 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.

All demographic and baseline characteristics except age of infant at enrollment stated above will be obtained from Phase III SPTL treatment studies.

Age of infant at enrollment is calculated in months between the date of birth and the date of enrollment in ARIOS study.

6.4. Medical Conditions (Current/Past)

Analyses of medical conditions (current/past) will be based on both populations as defined in Section 4, except where specified.

The number and percentages of subjects with newly diagnosed chronic medical conditions (respiratory, neurological, sensory, gastrointestinal, cardiovascular, renal conditions, and growth parameter) will be presented.

In addition, subject level listings of newly diagnosed chronic medical condition will be listed.

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

There is no efficacy analysis planned for this study.

7.2. Safety Analyses

All safety summaries will be performed for both populations as defined in Section 4. A listing of all safety data will be presented.

The primary objective of the planned analysis will be to use descriptive statistics to describe the safety and morbidity and mortality outcomes of children exposed to treatment during the Phase III SPTL studies investigating retosiban or comparator for the treatment of SPTL up to 24 months chronological age. The endpoints to be descriptively summarized are those described in Section 2.2. Descriptive statistics will be calculated by treatment group and/or time (up to 24 months chronological age), where appropriate.

For binary outcomes, all summary tables will include the number and percentage of subjects with the response/event. All summary tables will include N for each group (i.e., the total number of subjects in each treatment group).

The focus will be on collecting the safety outcomes as defined in the objectives (e.g., death) and serious AEs (SAEs), including congenital anomalies.

Nonserious AEs will not be tracked. All SAEs and safety outcomes will be followed until resolution, stabilization, or loss to follow-up.

7.2.1. Overview of Planned Analyses

The safety analyses will be based on both populations as defined in Section 4.

Table 3 provides an overview of the planned analyses with further details of data displays being presented in Appendix 8: List of Data Displays.

Table 3 Overview of Planned Safety Analyses

Endpoints	Observed			
	Summary		Individual	
	T	F	F	L
Newly Diagnosed Chronic Medical Condition	Y			Y
Adverse Events (AE)				
Serious Adverse Events	Y			Y
Death				Y
Infant Congenital Anomalies	Y			
Infant Neurodevelopment Assessments	Y			Y

Endpoints	Observed			
	Summary		Individual	
	T	F	F	L
Infant Neurodevelopment Impairment	Y			Y
Infant Hospital Utilization				Y

NOTES :

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

7.2.2. Adverse Events

Nonserious AEs will not be tracked.

7.2.2.1. Serious Adverse Events

SAEs 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, SAEs 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, SAEs 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 seriousness of an AE should be assessed by the Investigator independently from the severity of the AE. An 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, or is a congenital anomaly/birth defect.

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.

The number and percentage of subjects with any SAEs occurred before subjects reach 24 months chronological age will be summarized by treatment group in the tables. Within each group, SAEs will be summarized by frequency and proportion of total subjects, by event type, and by category of body system. A listing of SAEs will be provided.

7.2.2.2. Congenital Anomaly

Congenital anomaly reported in Phase III SPTL treatment studies, reported in ARIOS study (up to 1 year; after 1 year) will be summarized by treatment group. Congenital anomalies will be included in SAE listing.

7.2.2.3. Death

A listing of infant deaths will be provided.

7.2.3. Neurodevelopment Assessment at 9, 18, and 24 months

Neurodevelopment will be assessed by determining the proportions of infants diagnosed with developmental delays listed below at 9, 18, and 24 months of age, corrected for prematurity.

Endpoints related to Ages and Stages Questionnaire version 3 (ASQ-3) score and developmental evaluation described in Section 2.2 will be descriptively summarized at 9, 18, and 24 months by treatment group. For subjects with an ASQ-3 score in the black zone (>= 2 standard deviation [SD] below the mean) for any domain and referred for development evaluation, number of infants and percentage with Bayley Scales of Infant Development 3rd edition (BSID-III) and non-BSID-III results will be summarized. For subjects with an ASQ-3 score in the black zone for any domain, referred for development evaluation, but no assessment done, reason of no assessment done will be summarized. In addition to endpoints described in Section 2.2, number of infants and percentage with moderate or severe developmental delay using non BSID-III score will be summarized.

For BSID-III score, scaled scores for cognitive, receptive communication, expressive communication, fine motor, and gross motor will be derived from the subtest total raw scores and range from 1–19, with a mean of 10 and an SD of 3. Language composite scores will be derived from sums of receptive communication and expressive communication scaled scores. The composite score will be scaled to a metric with a mean of 100 and an SD of 15, and range from 40–160.

Endpoints related to Modified Checklist for Autism in Toddlers Revised with Follow-Up (M-CHAT-R/F) described in Section 2.2 will be descriptively summarized at 18, and 24 months by treatment group.

Endpoints related to Child Behavior Checklist for Ages 1.5 to 5 (CBCL/1.5-5) and cerebral palsy in Section 2.2 will be descriptively summarized at 24 months by treatment group.

Neurodevelopment assessment data will be presented in listings.

7.2.4. Neurodevelopment Assessment at 3, 4, and 5 years

New neurodevelopmental impairment from Question 8 in Modified Child Health Inventory (CHI) will be listed.

7.2.5. Neurodevelopment Impairment at the End of Study

Number of infants and percentage of neurodevelopment impairment endpoints and individual components will be summarized at the end of study (24 months). Individual components at the end of study are listed in in Section 2.2.

Motor composite score will be derived from fine motor and gross motor scaled scores in a similar fashion to language composite score described in Section 7.2.3

7.2.6. Health Outcome

Due to the early termination of the intervention studies (NEW-BORN 1 and ZINN) and the subsequent low enrolment in this study, exploratory health outcome data will only be provided in listings.

8. DEVIATION OF PLANNED ANALYSES FROM PROTOCOL

No changes will be made to the planned analyses after the breaking of the study blind.

9. REFERENCES

Bayley Scales of Infant and Toddler Development Third Edition, Copyright © 2006 by NCS Pearson, Inc.

10. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 10.1	Appendix 1: Protocol Deviation Definitions
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.2	Appendix 2: Time and Events
Section 10.3	Appendix 3: Treatment States and Phases
Section 10.4	Appendix 4: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.5	Appendix 5: Derived and Transformed Data • General, Study Population & Safety • Efficacy
Section 10.6	Appendix 6: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Other RAP Appendices	
Section 10.7	Appendix 7: Abbreviations & Trade Marks
Section 10.8	Appendix 8: List of Data Displays

10.1. 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. Summary of protocol deviation will not be presented.

10.2. Appendix 2: Time and Events

Event	28 Days Post EDD	Months							
		2	6	9	12	15	18	21	24
Written informed consent[1]	←	↔	↔	→					
Baseline characteristics and demographic data	X[2]								
RCC confirms and updates contact information from the parent/legal guardian	X								
Parent/legal guardian completes CHI[3]		X	X	X	X	X	X	X	X
RCC-PI follows up with HCP and reviews medical or other records to confirm parent-reported outcomes		→	→	→	→	→	→	→	→
RCC-PI reviews CHI results and refers to birth-defect evaluator based on results		→	→	→	→	→	→	→	→
Parent/legal guardian completes productivity questionnaire[4]									
Parent/legal guardian completes ASQ-3[6]			→	X[5]			X[5]		X[5] →
RCC-PI reviews ASQ-3 results and refers for developmental evaluation based on results[6]				→	→	→	→	→	→
Parent/legal guardian completes M-CHAT-R/F[7]							X		X
Parent/legal guardian completes CBCL/1.5–5[7]									X
RCC-PI refers child to specialist for cerebral palsy assessment (if required)[8]									X

ASQ-3 = Ages and Stages Questionnaire-3; CBCL/1.5–5 = Child Behavior Checklist for ages 1.5 to 5; CHI = Child Health Inventory; EDD = estimated date of delivery; HCP = health care provider; M-CHAT-R/F = Modified Checklist for Autism in Toddlers-Revised with Follow-Up; RCC = research coordinating center; RCC-PI = research coordinating center-principal investigator.

Note: All specified completion windows for applicable questionnaires (CHI, ASQ-3, CBCL/1.5–5, M-CHAT-R/F, and productivity) are provided to help standardize the data and avoid overlap. Information captured outside of these windows will be collected and analyzed separately, and questionnaires completed outside the completion window will not be considered protocol deviations.

1. Collected at the start of the Phase III spontaneous preterm labor (SPTL) treatment studies until the later date of either the date of discharge from the birth hospitalization or up to 9 months corrected age (to allow for the infant's 9-month CHI and ASQ-3 data collection).
2. Captured in Phase III SPTL treatment studies and combined with child follow-up data for analyses.
3. A positive response by the parent/legal guardian may trigger follow-up with the relevant HCP and/or medical record review for confirmation or more details on the condition or hospitalization. At each time point, the completion window of the CHI is +6 weeks.
4. Completed if infant has been treated by a specialist or has had an emergency room/urgent care or hospital visit. The completion window for the productivity questionnaire is +2 weeks from the date of completion of the relevant CHI.
5. Based on infant's corrected age. The completion window for the ASQ-3 is +30 days at Month 9 and ±30 days at Months 18 and 24.
6. If the parent/legal guardian receives a referral, then a qualified specialist will complete required assessments.
7. The CBCL/1.5–5 and M-CHAT-R/F questionnaires will be completed for all infants. The completion window for the CBCL/1.5–5 and M-CHAT-R/F is +6 weeks at 18 months (M-CHAT-R/F only) and +12 weeks at 24 months.
8. Referral will be made for infants who score in the black zone for the gross motor skills domain on the 24-month corrected age ASQ-3 and do not have an existing diagnosis of cerebral palsy.

10.3. Appendix 3: Treatment States and Phases

Not applicable.

This is a safety follow-up study of infants and children exposed to treatment during their mother's participation in a Phase III SPTL treatment study of retosiban or comparator for SPTL. Infants and children enrolled in this study will not be administered any investigational product.

10.4. Appendix 4: Data Display Standards & Handling Conventions

10.4.1. Study Treatment & Sub-group Display Descriptors

Study Treatment Descriptions		
Code	**Description**	**Order of Table Presentation**
1	Retosiban (Combined)	4
2	ZINN Atosiban	2
3	NEWBORN-1 Placebo	1
2, 3	Comparators (Combined)	3

10.4.2. Baseline Definition

Baseline characteristics and demographic data will be captured from the Phase III SPTL treatment studies and combined with child follow-up data for analyses. For all endpoints in ARIOS study, baseline value is not required for analysis.

10.4.3. 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 1.1. • 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

Formats
• For safety analyses, all data will be reported according to the actual treatment the mother received. • 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 and formal statistical analyses :
  • 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 for mother 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 summaries and statistical analyses.

Unscheduled Visits
• 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.

10.5. Appendix 5: Derived and Transformed Data

10.5.1. 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. • Unscheduled visit will be included in the listings.
Study Day
• Calculated as the number of days from the first study treatment date for mothers : [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 Note: All assessments should be done after the first study treatment date for mothers.

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

10.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion status is defined as subjects who are prematurely withdrawn. • Subjects who are withdrawn from study participation after enrolment in ARIOS study will not be replaced.

10.6.2. 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. • For disposition and demographic data, no imputation will be done. • For safety and neurodevelopment data, it will be assumed that the events of interest did not occur.

10.6.2.1. Handling of Missing/Partial Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays. No imputation will be applied.

10.7. Appendix 7: Abbreviations & Trade Marks

10.7.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
ASQ-3	Ages and Stages Questionnaire version 3
BMI	Body mass index
BSID III	Bayley Scales of Infant Development 3rd Edition
CBCL/1.5-5	Child Behaviour Checklist for Ages 1.5-5
CHI	Child Health Inventory
CSR	Clinical Study Report
eCRF	electronic Case Report Form
EDD	Estimated Date of Delivery
FMM	Finite Mixture Models
GA	Gestational Age
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
MedDRA	Medical Dictionary for Regulatory Activities
M-CHAT-R/F	Modified Checklist for Autism in Toddlers Revised with Follow-Up
RAP	Reporting and Analysis Plan
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
SPTL	Spontaneous Preterm Labor

10.7.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

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10.8. Appendix 8: List of Data Displays

A separate document for shells contains all table, listing and figures' (TLFs) for the planned final analysis.

10.8.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	10.1 to 10.4	
Safety	10.5, 20.5, 10.6, 20.6	
Other Analysis	10.7, 20.7, 10.8, 20.8, 10.10, 20.10, 10.11, 20.11	
Section	**Listings**	
ICH Listings	37, 38, 42 to 44	
Other Listings	39 to 41, 45, 46	

10.8.2. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
10.1	Infant Safety		Infant Subject Disposition		
10.2	Infant Safety		Number of Infants Enrolled at Milestone		
Demographics					
10.3	ARIOS Safety		Infant Subject Demographic and Baseline Characteristics		
10.4	ARIOS Safety		Summary of Subject Race and Racial Combinations		
Medical Condition					
10.6	Infant Safety		Newly Diagnosed Chronic Medical Condition		
20.6	ARIOS Safety		Newly Diagnosed Chronic Medical Condition		

10.8.3. Safety Tables

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
10.5	Infant Safety		Summary of Infant Serious Adverse Events		
20.5	ARIOS Safety		Summary of Infant Serious Adverse Events		
Neurodevelopment Assessments					
10.7	Infant Safety		Neurodevelopment Assessments (ASQ-3 and BSID-III scores) at 9, 18 and 24 Months		
20.7	ARIOS Safety		Neurodevelopment Assessments (ASQ-3 and BSID-III scores) at 9, 18 and 24 Months		
10.8	Infant Safety		Neurodevelopment Assessments (CBCL/1.5-5. M-CHAT-R/F, Cerebral Palsy or Behavioral Specialist) at 18 and 24 Months		
20.8	ARIOS Safety		Neurodevelopment Assessments (CBCL/1.5-5. M-CHAT-R/F, Cerebral Palsy or Behavioral Specialist) at 18 and 24 Months		
10.9	Infant Safety		Neurodevelopment Impairment at the End of Study (24 Months)		
20.9	ARIOS Safety		Neurodevelopment Impairment at the End of Study (24 Months)		
Congenital Anomaly					
10.10	Infant Safety		Summary of Congenital Anomaly		
20.10	ARIOS Safety		Summary of Congenital Anomaly		

10.8.4. ICH Listings

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
37	ARIOS Safety		Study Disposition		
Demographics					
38	ARIOS Safety		Demographic and Baseline Characteristics		
43	ARIOS Safety		Race and Racial Combinations		
Adverse Events					
42	ARIOS Safety		Infant Serious Adverse Events		
44	ARIOS Safety		Infant Deaths		

10.8.5. Non-ICH Listings

Non-ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Medical Condition					
39	ARIOS Safety		Newly Diagnosed Chronic Medical Conditions		
Health Outcome					
46	ARIOS Safety		Infant Hospital Utilization		
Neurodevelopment					
40	ARIOS Safety		Neurodevelopment Assessments at 9, 18 and 24 Months		
41	ARIOS Safety		Neurodevelopment Assessments at 3, 4 and 5 Years		
45	ARIOS Safety		Developmental Evaluation		