TITLE PAGE

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Title:	Follow-Up Study to Assess Long-Term Safety and Outcomes in Infants and Children Born to Mothers Participating in Retosiban Treatment Studies

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2014N194466_00	2014-MAY-14	Original
2014N194466_01	2015-AUG-17	Amendment No. 1
The following changes are reflected in Protocol Amendment No. 1: • Extend the study duration from 24 months to 5 years to identify any potential neurodevelopmental and behavioral disorders through annual assessments at years 3, 4, and 5, specifically autism and attention deficit hyperactivity disorder. • Add an assessment using a modified version of the CHI questionnaire at 3, 4, and 5 years of the child's chronological age to collect data to identify any potential neurodevelopmental and behavioral disorders. • Add an additional assessment of the M-CHAT-R/F at 18 months (corrected age) per American Academy of Pediatrics guidelines • Revise to indicate that the M-CHAT-R/F (assessed at 18 and 24 months) and the CBCL/1.5-5 (assessed at 24 months) are mandatory for all infants, regardless of ASQ-3 results, per American Academy of Pediatrics guidelines • Remove as a neurodevelopment endpoint the proportion of infants referred for an additional behavior assessment using the M-CHAT-R/F and CBCL/1.5-5 • Clarify that any infant serious adverse events (SAEs) and/or AEs of special interest that were unresolved at the end of the Phase III treatment studies and any new SAEs reported during this study should be followed to stabilization or resolution in those children participating in the follow-up study. • Revise the subgroups that may be included in the safety analyses to reflect study design of Phase III SPTL Study 200719 (NEWBORN-1) • Clarify unblinding text to indicate that there is no requirement for the investigator to discuss unblinding with the PPD medical monitor in order to rapidly unblind a child's treatment assignment, if needed • Incorporate other administrative changes		
2014N194466_02	2018-NOV-01	Amendment No. 2
The following changes are reflected in Protocol Amendment No. 2: • Reduction of study duration from 5 years to 24 months due to: – Termination of the retosiban development program, such that there will be no further in utero exposure to retosiban, and hence safety data from this ongoing study will not inform the potential risk for future use of retosiban. – Low recruitment for interventional studies 200719 (NEWBORN-1) and		

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200721 (ZINN). Hence, the number of infants exposed to retosiban in utero and included in the current (200722) study is small.

  - The independent data monitoring committee (IDMC) recommendation that the neonatal follow-up be limited to 24 months of age given no safety issues detected in their unblinded review of available 200722 data and also that statistical analysis at a 5-year timepoint would not provide any meaningful results due to the small number of enrolled subjects.

- Reclassification of all resource utilization endpoints as exploratory endpoints due to the reduced sample size
- Correction of an error in the mean BSID-III score for the cognitive impairment, fine motor and gross motor scales to <4 to reflect that these are not composite scores
- Incorporation of other administrative changes

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November 1st, 2018

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Regulatory Agency Identifying Number(s):

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RCC-PI PROTOCOL AGREEMENT PAGE

For protocol 200722 (ARIOS)

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

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

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

RCC-PI Name:		
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RCC-PI Phone Number:		
RCC-PI Signature		Date

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LIST OF ABBREVIATIONS AND DEFINITIONS

AE	adverse event
ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
ASEBA	Achenbach System of Empirically Based Assessment
ASD	autism spectrum disorder
ASQ-3	Ages and Stages Questionnaire-3
BSID-III	Bayley Scale for Infant Development, third edition
CBCL/1.5–5	Child Behavior Checklist for Ages 1.5 to 5
CDC	Centers for Disease Control and Prevention
CHI	Child Health Inventory
CI	confidence interval
CV	cardiovascular
DSM	Diagnostic and Statistical Manual
eCRF	electronic case report form
eDC	electronic data capture
EDD	estimated date of delivery
EPDS	Edinburgh Postnatal Depression Scale
ER/UC	emergency room/urgent care
EUROCAT	European Surveillance of Congenital Anomalies
FSFV	first subject first visit
GCP	Good Clinical Practice
GMFCS	Gross Motor Functional Classification System
HCP	health care provider
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICU	intensive care unit
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
kg	kilogram
MACDP	Metropolitan Atlanta Congenital Defects Program
M-CHAT-R/F	Modified Checklist for Autism in Toddlers-Revised with Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
NICU	neonatal intensive care unit
PI	principal investigator
PICU	pediatric intensive care unit
RAP	reporting and analysis plan
RCC	research coordinating center
RCC-PI	research coordinating center-principal investigator
SAE	serious adverse event
SPM	Study Procedures Manual
SPTL	spontaneous preterm labor

DEFINITIONS

Child	Aged from 2 years to up to 12 years, per definition of the US Food and Drug Administration
Chronological age	Defined as the time elapsed after birth; it is usually described in days, weeks, months, and years
Corrected age	Calculated by subtracting the number of weeks an infant is born before $40^{0/7}$ weeks' gestation from the chronological age. This term is used to describe children up to 3 years of age who were born preterm.
End of the Phase III SPTL treatment studies	The cut-off date for final review of the neonatal record, signifying the end of Phase III spontaneous preterm labor (SPTL) treatment studies, is the estimated date of delivery (EDD) plus 28 days; this is referred to as 28 days post EDD
Estimated date of delivery	Defined as $40^{0/7}$ weeks' gestation for all subjects in the Phase III SPTL treatment studies
Gestational age	Determined by (1) known fertilization date, either *in vitro* fertilization or intrauterine insemination, (2) last menstrual period confirmed by the earliest ultrasound prior to $24^{0/7}$ weeks' gestation, or (3) the earliest ultrasound alone prior to $24^{0/7}$ weeks' gestation, whichever is the most accurate method available for each subject in the Phase III SPTL treatment studies
Infant	Aged from 1 month to up to 2 years, per definition of the US Food and Drug Administration

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PROTOCOL SUMMARY

Rationale

Advances in perinatal intensive care have resulted in increased survival rates for high risk newborns but limited improvement in morbidity. The immaturity of organs, such as the brain, lungs, and gastrointestinal tract, render these newborns susceptible to injury and abnormal development and function, which often leads to long-term health problems and disability. The risk for medical disability is inversely related to the gestational age at birth; the most common disabilities include cerebral palsy, cognitive dysfunction, blindness and impaired vision, hearing loss, and disorders of psychological development (i.e., behavior and emotion).

Over the past decades, few medical interventions have been designed to prevent preterm birth and/or reduce the severity of prematurity complications. Such treatments may also improve long-term outcomes. One of the major advances in perinatal medicine has been the finding that antenatal corticosteroids given to women at risk of imminent preterm birth reduces the risks for neonatal mortality and morbidity. Corticosteroids now represent the standard of care for an acute antenatal intervention to improve neonatal outcomes in the developed world [RCOG, 2011; ACOG, 2012].

However, there is an increasing awareness that the intended beneficial effects of perinatal interventions do not necessarily correlate with long-term outcomes. Dexamethasone in high daily doses appears to reduce mortality and the incidence of bronchopulmonary dysplasia but treatment is associated with numerous short- and long-term adverse outcomes, including neurodevelopmental impairment. As a result, treatment with high dose dexamethasone is not recommended [Watterberg, 2010]. The ORACLE II Study is an example of a perinatal treatment that was associated with adverse long-term outcomes and no neonatal benefit. ORACLE II studied the effect of antibiotics to improve neonatal outcomes in women with spontaneous preterm labor (SPTL) with intact membranes and no evidence of clinical infection. No reduction in neonatal complications was observed. However, the long-term follow-up revealed an increase in functional impairment and a higher risk for cerebral palsy in children whose mothers had received antibiotics [Kenyon, 2001; Kenyon, 2008]. These observations have led to an appreciation that perinatal interventions may affect growth and development and have highlighted the importance of long-term safety and outcome studies after randomized, controlled studies of perinatal interventions.

The goal of this study (ARIOS), therefore, is to assess the safety and outcomes of infants and children who were exposed to retosiban (GSK221149) or comparator in utero in the Phase III SPTL treatment studies and provide assurance that treatment is not associated with significant adverse outcomes in early childhood.

In May 2017, the corresponding treatment trials 200719 (NEWBORN-1, placebo comparison) and 200721 (ZINN, atosiban comparison) were terminated early due to poor recruitment and the length of time needed to complete the studies. The placebo-controlled trial enrolled only 23 of the target 900 participants over 17 months, and the atosiban comparator trial enrolled 97 of the target 330 participants over 29 months. Maternal,

fetal, and neonatal adverse events were no more common with retosiban than placebo or atosiban. The development program was subsequently terminated with no further in utero exposure of retosiban planned.

Objectives

The study objective is to assess the safety and outcomes in infants and children who were exposed to retosiban or comparator in the Phase III SPTL treatment studies.

Specific objectives include the following:

Primary

- 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
- To characterize the clinical safety in terms of neurodevelopment in infants and children exposed to retosiban or comparator in utero

Exploratory

- To characterize parental productivity loss related to a sick child and infant resource utilization in terms of hospital admissions, length of stay, emergency room/urgent care (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

Study Design

ARIOS is a long-term infant and child follow-up study that will 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. The final assessment of the Phase III SPTL treatment studies is a collection of neonatal morbidity data and will occur at 28 days after the estimated date of delivery (EDD), where EDD is defined as $40^{0/7}$ weeks' gestation. After this time, infants become eligible for this follow-up study. Ideally, the Phase III SPTL study investigators will obtain consent and medical release for this study when the women's acute episode of preterm labor has resolved and prior to discharge from the hospital for the treatment of preterm labor. The infant will be able to be consented into the study until the later date of either the date of discharge from the birth hospitalization or up to 9 months corrected age. Infants and children will be followed at prespecified intervals until they have reached 24 months chronological age. This study does not require medical interventions or study visits to an investigational site. Instead, parents or legal guardians will be prompted at certain time points to complete developmental questionnaires and other data regarding their child's health status via an electronic device. Data collected during this follow-up study will be managed by a centralized research coordinating center (RCC). Regionally based pediatricians will serve as the study principal investigators (referred to as RCC-PIs) for the follow-up study. All communications the RCC-PI has with the parent/legal guardian or the child's health care provider (HCP) will occur remotely; there will be no clinic visits.

The child's parent/legal guardian will be asked to complete a Child Health Inventory (CHI) at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age. The CHI questionnaire completed up to the 24-month time point will screen for infant mortality and morbidity and will capture data on resource utilization. If the parent/legal guardian indicates that the child has been newly diagnosed (after 28 days post EDD) with chronic conditions or congenital anomalies, follow-up by the RCC-PI will be undertaken with the applicable HCP to confirm the parent report. Persistence or resolution of conditions will be determined in subsequent questionnaires after the initial report.

If the parent/legal guardian indicates that the child has had a hospital visit or surgery or that the child has died, the RCC-PI will confirm by obtaining medical and other records from HCPs or medical facilities, including a death certificate, if applicable. If the parent/legal guardian indicates that the child has had an ER/UC visit, the RCC-PI will use discretion and obtain medical records when the reported indication suggests a true emergency. Additional details regarding ER/UC visits will be provided in the Study Procedures Manual. After review of all records, the RCC-PI may request additional targeted follow-up data from the relevant HCP or medical facility if clarification is needed on any reported study endpoints or serious adverse events.

During the 24 months of participation in the study, if the parent/legal guardian indicates that the infant has been treated by specialists or has had ER/UC visits or hospitalizations, he/she will be asked to complete a productivity questionnaire to evaluate loss of parental productivity.

When a congenital anomaly is reported, it will be reviewed by an expert in teratology who is engaged by the RCC-PI to serve as the birth defect evaluator for this study. The birth defect evaluator's responsibilities will include the review, evaluation, and classification of all reports of birth defects.

To screen for a delay in the areas of communication, gross motor, fine motor, problem-solving, and personal-social skills, the parent/legal guardian will be asked to complete the 9-, 18-, and 24-month Ages and Stages Questionnaire-3 (ASQ-3) when the infant's corrected age corresponds to 9, 18, and 24 months; for example, parents/legal guardians of an infant born 3 months premature will complete the 9-month ASQ-3 at 12 months chronological age. Any child with a score in the black zone (≥2 SD below the mean) in any of the 5 domains of the ASQ-3 will be referred to a qualified assessor for a developmental evaluation (e.g., using the Bayley Scale for Infant Development, third edition [BSID-III]), unless the child is already under the care of a specialist who has recently conducted a BSID-III evaluation. Based on results from the ASQ-3 administered at 24 months corrected age and if no cerebral palsy diagnosis has been made to date, the infant may be referred to a qualified examiner for a formal assessment of cerebral palsy.

The Modified Checklist for Autism in Toddlers–Revised with Follow-Up (M-CHAT-R/F) will be completed for all infants at 18 and 24 months (corrected age) and the Child Behavior Checklist for Ages 1.5 to 5 (CBCL/1.5–5) will be completed for all infants at 24 months (corrected age) to assess the risk for other behavioral problems or autism spectrum disorder (ASD). If at any of these time points a child has an M-CHAT-R/F score that indicates further evaluation is required and/or a CBCL/1.5–5

score above the 97th percentile for a subset of prespecified questions, the child will be referred to a specialist for a formal assessment.

Study Endpoints/Assessments

Study primary endpoints include the following and are further defined in Section 6.2.2:

Morbidity and mortality endpoints:

- 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
  - Neurological conditions
  - Sensory conditions
  - Gastrointestinal conditions
  - Cardiovascular conditions
  - Renal conditions
  - Growth parameters
- Proportion of infants and children with newly diagnosed (after 28 days post EDD) congenital anomalies
- Proportion of infant and child deaths after 28 days post EDD and until 24 months chronological age

Neurodevelopment 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 impairment (<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)
  - 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, attention deficit disorder (ADD), or attention deficit hyperactivity disorder (ADHD)

Exploratory resource utilization endpoints include:

- 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., neonatal intensive care unit [NICU], Pediatric, pediatric intensive care unit [PICU], Nursery level 3, intensive care unit [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.

1. INTRODUCTION

1.1. Background

Gestational age at birth is considered the most important predictor of a newborn's subsequent health and survival. Infants born too early and too small have a much greater risk of death and both short- and long-term disability than those born at term [Saigal, 2008]. Early morbidity due to prematurity includes respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and sepsis. Late consequences of prematurity include chronic lung disease, cerebral palsy, sensory impairment, and cognitive deficits. An estimated 14.9 million babies were born prematurely in 2010, representing 11% of all live births worldwide [Blencowe, 2012]. Preterm birth rates ranged from approximately 5% in several European countries to 18% in some African countries. In 2013, nearly 450 000 preterm births, defined as childbirth occurring before 37 completed weeks' gestation, occurred in the United States [Martin, 2015]. These preterm infants had an infant mortality rate approximately 15 times the rate for full-term infants; the highest infant mortality rate occurs in infants born prior to 32 weeks' gestation [Matthews, 2010]. Although the risk for complications decreases with increasing gestational age, infants born just a few weeks before term carry an increased risk for developing medical complications, resulting in excessive mortality and morbidity rates during the birth hospitalization, as compared with the rates in full-term infants [Engle, 2007].

Prematurity directly influences the level of medical care, length of hospitalization, and associated costs; prematurity sequelae extend the need for continued medical care into childhood. Estimates for 2005 placed the annual economic cost in the United States at a minimum of 26.2 billion dollars or 51 600 dollars per infant born preterm; roughly two-thirds of this cost was for medical care [Behrman, 2007].

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

Retosiban (GSK221149) is a potent, competitive, and highly selective oxytocin receptor antagonist. Retosiban inhibits spontaneous and oxytocin-induced contractions in human myometrial tissue. Retosiban was being developed for the treatment of spontaneous preterm labor (SPTL) in women with intact membranes.

Phase III SPTL treatment studies were conducted to demonstrate the ability of retosiban to prolong pregnancy and improve neonatal health, as well as to describe the maternal, fetal, and neonatal safety profiles. The treatment studies were terminated due to limited

recruitment and the development program was subsequently terminated with no further in utero exposure planned.

1.1.1. Previous Human Experience

Retosiban has been administered to 219 healthy subjects. A review of the safety data in these healthy subjects showed no effects on vital signs, electrocardiogram parameters, or laboratory values that were attributable to study drug.

No clinically significant adverse events (AEs) or serious AEs (SAEs) have been reported in the completed Phase I studies of healthy volunteers.

Study OTA105256 was the first Phase II clinical study of retosiban in preterm labor (n=93) [Thornton, 2015; GlaxoSmithKline Document Number CM2006/00201/06]. The study was designed to investigate the safety and dose response of retosiban given intravenously to women with intact membranes in preterm labor between $30^{0/7}$ and $35^{6/7}$ weeks of gestation. Final results showed that intravenous retosiban treatment was associated with a significant difference in days to delivery and significant reduction in preterm births. The mean difference in days to delivery was 8.2 days relative to placebo (95% credible interval: 2.7, 13.74). Median prolongation of pregnancy was 35 days in women treated with retosiban, compared with 25 days in women assigned to the placebo group. The treatment difference was consistent across gestational ages. The proportion of preterm births was 18.7% in the retosiban group and 47.2% in the placebo group. The relative risk for preterm birth in the retosiban group was 0.38 (95% credible interval: 0.15, 0.81).

The Phase 3 program included 2 global blinded, randomized, controlled trials (200721 [ZINN] and 200719 [NEWBORN-1]) and a single infant follow-up trial (200722 [ARIOS]). Eligible subjects were aged 12 to 45 years with an uncomplicated singleton pregnancy and intact membranes in spontaneous preterm labor at $24^{0/7}$ to $33^{6/7}$ weeks' gestation. ZINN (N=330) aimed to show superiority of retosiban (IV) over atosiban on time to delivery (first subject first visit [FSFV] was March 2015). NEWBORN-1 (N=900) was designed to demonstrate neonatal benefit (based on a composite endpoint) as well as time to delivery or time to treatment failure over placebo (FSFV February 2016). The intervention trials were terminated early on 11 May 2017 because of slow recruitment and the retosiban project was discontinued permanently. Last subject last visit (LSLV) was 24 July 2017 for NEWBORN-1 and 25 August 2017 for ZINN. Meaningful analyses of these well-controlled trials could not be performed due to small numbers of completing participants. Mean time to delivery or treatment failure in the placebo-controlled trial was 18.9 days with retosiban (n=10) versus 11.1 days with placebo (n=13). Two neonates in the retosiban and 4 in the placebo group had ≥1 component of the neonatal composite endpoint. The adjusted mean time to delivery in the atosiban comparator trial was 32.51 days with retosiban (n=50) compared with 33.71 days with atosiban (n=47; $P>0.05$). Maternal, fetal, and neonatal AEs were no more common with retosiban than placebo or atosiban.

In NEWBORN-1, 1 participant in the retosiban group provided cord blood and breast milk samples; retosiban was found in both (cord blood, 1.9 µg/L; breast milk, 3.6 µg/L).

In ZINN, 12 women in the retosiban group provided cord blood samples, none of which had detectable levels of retosiban. One participant also provided a breast milk/colostrum sample. The retosiban concentration was 0.3 µg/L.

1.2. Rationale

Advances in perinatal intensive care have resulted in increased survival rates for high risk newborns but limited improvement in morbidity. The immaturity of organs, such as the brain, lungs, and gastrointestinal tract, render these newborns susceptible to injury and abnormal development and function, which often leads to long-term health problems and disability. The risk for medical disability is inversely related to the gestational age at birth; the most common disabilities include cerebral palsy, cognitive dysfunction, blindness and impaired vision, hearing loss, and disorders of psychological development (i.e., behavior and emotion).

Over the past decades, few medical interventions have been designed to prevent preterm birth and/or reduce the severity of prematurity complications. Such treatments may also improve long-term outcomes. One of the major advances in perinatal medicine has been the finding that antenatal corticosteroids given to women at risk of imminent preterm birth reduces the risks for neonatal mortality and morbidity. Corticosteroids now represent the standard of care for an acute antenatal intervention to improve neonatal outcomes in the developed world [ACOG, 2012; RCOG, 2011].

However, there is an increasing awareness that the intended beneficial effects of perinatal interventions do not necessarily correlate with long-term outcomes. Dexamethasone in high daily doses appears to reduce mortality and the incidence of bronchopulmonary dysplasia but treatment is associated with numerous short- and long-term adverse outcomes, including neurodevelopmental impairment. As a result, treatment with high-dose dexamethasone is not recommended [Watterberg, 2010]. The ORACLE II Study is an example of a perinatal treatment that was associated with adverse long-term outcomes and no neonatal benefit. ORACLE II studied the effect of antibiotics to improve neonatal outcomes in women with SPTL with intact membranes and no evidence of clinical infection. No reduction in neonatal complications was observed. However, the long-term follow-up revealed an increase in functional impairment and a higher risk for cerebral palsy in children whose mothers had received antibiotics [Kenyon, 2001; Kenyon, 2008]. These observations have led to an appreciation that perinatal interventions may affect growth and development and have highlighted the importance of long-term outcome studies after randomized, controlled studies of perinatal interventions.

The goal of this study (ARIOS), therefore, is to assess the safety and outcomes of infants and children who were exposed to retosiban or comparator in utero in the Phase III SPTL treatment studies and provide assurance that treatment is not associated with significant adverse outcomes in early childhood.

1.3. Benefit:Risk Assessment

Summaries of findings from both clinical and nonclinical studies conducted with GSK221149 can be found in the IB and the Phase III SPTL treatment clinical study

reports. The following section outlines the risk assessment and mitigation strategy for this protocol.

1.3.1. Risk Assessment

This study is a follow-up safety study of infants and children exposed to treatment while in utero 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; therefore, there are no anticipated or known risks to the infants and children who participate in this safety study.

The intent of this study is to ensure there have been no unintended consequences to the infants and children from exposure to retosiban or comparator during their mother's participation in the Phase III clinical study of retosiban, specifically with respect to the following:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Fetal exposure through placental transfer	For both NEWBORN-1 and ZINN, cord blood samples were requested from subjects who delivered at the investigative center within 12 hours after discontinuation of study drug. Samples were only analyzed for subjects randomized to retosiban. A total of 4 cord samples were collected within NEWBORN-1 (3 placebo: 1 retosiban) and 27 within ZINN (12 retosiban: 15 atosiban). Within both studies, only 1 cord blood sample tested positive for retosiban at a concentration of 1.9 µg/L. The 1.9 µg/L is approximately 0.006x to 0.01x the cord blood concentrations that were observed in the pregnant monkey toxicity studies (cord blood concentrations = 159 to 313 µg/L). There were no adverse effects observed in the offspring in monkey studies, where growth and development included a full assessment of reflexive behaviors, infant ECG and blood chemistry were analyzed. Furthermore, a rat post-natal study starting in juvenile rats that were 1 day old did not show any adverse effects on growth and development, including neurobehavior and reproductive assessments at exposure levels that were approximately 800-fold of what was observed in the cord blood (gender averaged Cmax = 1535 µg/L). Day 1 old rats were used in this study as they were developmentally similar to late third term human fetuses. The overall animal data indicate that potential risk for a fetus exposed gestationally to retosiban is negligible.	Analysis of maternal blood and cord blood samples was performed to test for levels of retosiban in women who delivered at an investigative center within 12 hours of the completion of study treatment infusion as part of the Phase III SPTL treatment studies. Surveillance for signals indicating adverse fetal or neonatal effects with in utero exposure to retosiban will be performed throughout this study. Infants exposed to retosiban in utero will be followed for up to 24 months in this study to assess safety and neurodevelopmental outcomes.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Neonatal exposure via breast milk	Positive breast milk samples were detected within 1 maternal subject in NEWBORN-1 and 1 subject in ZINN, with the highest concentration being 0.36 µg/L. Assuming a standardized milk consumption of 0.150 L/kg/day (the mean milk intake of a fully breast-fed 2-month old infant [Begg, 1999; Bennett, 1988; Hagg, 2000; Kristensen, 1999]), the worst-case dose of retosiban that a breast-fed child would be exposed to is 0.54 µg/kg/day (3.6 µg/L x 0.15 L/kg/day). This is approximately 0.5% of the human dose. This is the worst-case scenario because the mother is not being administered retosiban post-partum during the lactation period, and retosiban is cleared rapidly, which would rapidly diminish the amount retosiban present circulation and in the milk. Furthermore, based on body surface area, this potential infant dose is greater than 8000-fold, the dose where no adverse effects were seen in growth and development in the rat post-natal development study (rat post-natal development study NOAEL = 30 mg/kg/day; human equivalent dose = 4800 µg/kg/day). The potential lactational dose of retosiban that would therefore pose any significant risk to a newborn is negligible.	Breast milk/colostrum samples were collected for measurement of retosiban when delivery occurred and lactation had started within 12 hours of receiving study treatment infusion as part of the Phase III SPTL treatment studies. Infants exposed to retosiban via breast milk will be followed for up to 24 months in this study to assess safety and neurodevelopmental outcomes.

ECG = electrocardiogram; NOAEL = no-observed-adverse-effect-level; SPTL = spontaneous preterm labor.

1.3.2. Benefit Assessment

Babies born prematurely are at risk for death, short-term medical complications, long-term disabilities, and developmental problems; these risks are inversely related to gestational age. Although babies born before 32 weeks have the greatest risk for death and poor health outcomes [Saigal, 2008; Lundqvist, 2009; Matthews, 2010], late preterm infants (defined as $34^{0/7}$ to $36^{6/7}$ weeks) are now known to carry a higher risk of morbidity and mortality than term infants [Engle, 2007]. Approximately 40% to 45% of preterm births are preceded by SPTL; the remainder is associated with preterm premature rupture of membranes and clinical indications for delivery [Romero, 2000; Goldenberg, 2008].

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

Given the inverse relationship between the risks for prematurity complications and gestational age at birth, the development of a treatment that significantly prolongs pregnancy in women with SPTL would be invaluable if associated with improved perinatal outcomes. Results from the Phase II study OTA105256 offer hope that retosiban may prolong pregnancy to such a degree that perinatal outcomes could be favorably affected [Thornton, 2015]. However, the results from the Phase III interventional studies did not provide compelling evidence that retosiban could prolong time to delivery of retosiban relative to placebo or atosiban, but because of the low enrollment numbers and inadequate statistical power, results should be interpreted with caution.

The benefit to infants and children participating in this study is the focus on following morbidity and neurodevelopment for up to 24 months following exposure to retosiban or comparator medication. Participating infants and children will have the benefit of access to developmental screening (Ages and Stages Questionnaire-3 [ASQ-3], Child Behavior Checklist for Ages 1.5 to 5 [CBCL/1.5–5], and the Modified Checklist for Autism in Toddlers–Revised with Follow-Up [M-CHAT-R/F]), which may not be routinely provided and will allow parents/legal guardians to monitor and track the child's developmental milestones in a formalized manner. In addition, screening results may be shared with the child's physician (HCP or other) as requested by the parent/legal guardian. In the event a potential issue is identified and further follow-up is warranted, the child will be referred to developmental specialists/qualified assessors for further evaluations as part of this study. In this manner, neurodevelopmental issues may be identified earlier than would have been normally.

1.3.3. Overall Benefit:Risk Conclusion

For detailed information on the identified risks and benefit:risk assessment of retosiban, refer to the Investigator's Brochure (IB) [GlaxoSmithKline Document Number CM2006/00201/06]. The overall benefit:risk assessment of retosiban appears favorable for the mother and fetus/infant.

2. OBJECTIVES

The study objective is to assess the safety and outcomes in infants and children who were exposed to retosiban or comparator in the Phase III SPTL treatment studies. Table 1 summarizes the specific study objectives and the corresponding endpoints, which are described in detail in Section 6.2 (Safety) and Section 6.3 (Health Outcomes).

Table 1 Summary of Study Objectives and Corresponding Endpoints

Objective	Endpoints
Primary	

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

Objective	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)
	  • 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

Objective	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.

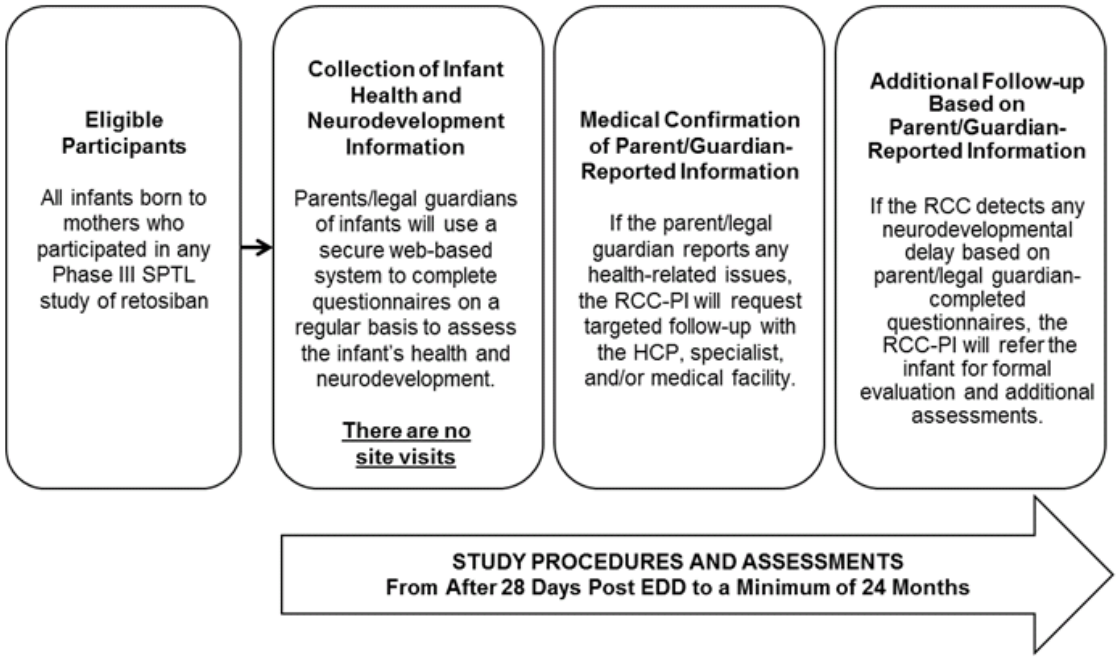
3. INVESTIGATIONAL PLAN

3.1. Study Design

ARIOS is a long-term infant and child follow-up study that will 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. The final assessment of the Phase III SPTL treatment studies is a collection of neonatal morbidity data and will occur at 28 days after the EDD, where EDD is defined as $40^{0/7}$ weeks' gestation. The end date of the Phase III SPTL treatment studies is referred to as 28 days post EDD. Either the obstetrician investigators or neonatologist subinvestigators from the Phase III SPTL studies or their delegate will be responsible for obtaining consent for the infant to participate in the follow-up study; they also will be responsible for obtaining the signed medical release forms from all hospitals and HCPs providing follow-up care to the infant. Ideally, the Phase III SPTL study investigators will obtain

consent and medical release when the woman's acute episode of preterm labor has resolved and prior to discharge from the hospital for the treatment of preterm labor. The infant will be allowed to be consented into the study 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 Child Health Inventory [CHI] and ASQ-3 data collection) via follow-up contact from the research coordinating center-principal investigator (RCC-PI) to the parent/legal guardian. This follow-up contact and informed consent discussion may occur via telephone with signed consent and medical releases transmitted via mail or courier. Infants and children will be followed at prespecified intervals until they reach 24 months chronological age (see Table 2). This study does not require medical interventions or study visits to an investigational site. Instead, 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. Data collected during this follow-up study will be managed by a centralized RCC. Regionally based pediatricians will serve as study principal investigators (referred to as RCC-PIs) for this study. All communications the RCC-PI has with the parent/legal guardian or the child's HCP will occur remotely; there will be no clinic visits. An overview of the study design is shown in Figure 1.

Figure 1 Study Design



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

Electronic data capture (eDC) tools and processes including electronic case report forms (eCRF) and electronic patient-reported outcome devices will allow entry of data, regardless of when it is obtained. If at any time the data suggest any developmental delay, the RCC-PI will refer the child to a specialist (if not already under the care of a specialist) for formal evaluation and additional assessments. The child's local primary care pediatric

provider will be asked to provide routinely available data on the child to the RCC. Additional contacts may occur at the discretion of the RCC personnel to complete the data collection.

The child's parent/legal guardian will be asked to complete the CHI at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age. The CHI questionnaire completed up to the 24-month time point will screen for infant mortality and morbidity and will capture data on resource utilization. If the parent/legal guardian indicates that the child has been newly diagnosed (after 28 days post EDD) with chronic conditions or congenital anomalies, follow-up will be undertaken with the applicable HCP to confirm the parent/legal guardian report. Persistence or resolution of conditions will be determined in subsequent questionnaires after the initial report. If protocol-specific evaluations are in progress at the end of the child's protocol-defined participation in this study (24 months chronological age) and results have not yet been received or reported, the time period may be extended to collect those reports.

If the parent/legal guardian indicates that the child has had any emergency room/urgent care (ER/UC) visits, he/she will be asked to record the number of visits and to indicate if the visit resulted in hospitalization. If the parent/legal guardian indicates that the child has been hospitalized or has had any surgeries, medical records from the applicable medical facility will be obtained and abstracted for pertinent details, including principal and secondary discharge diagnoses, type of hospital unit admitted to (e.g., neonatal intensive care unit [NICU], Pediatrics, pediatric intensive care unit [PICU], Nursery level 3, ICU), and length of stay. If the parent/legal guardian indicates that the child died after 28 days post EDD, details of the death will be obtained from the death certificate or appropriate HCP or medical records if the death certificate is not available. Note that all infant deaths that occur before 28 days post EDD will be captured and reported as part of the Phase III SPTL treatment studies.

During the 24 months of participation in the study, if the parent/legal guardian indicates that the infant has been treated by specialists or has had ER/UC visits or hospitalizations, he/she will be asked to complete a productivity questionnaire to evaluate loss of parental productivity.

The RCC-PI will review all data including medical records, death certificates, data provided by the parent/legal guardian, and any follow-up confirmatory data provided by HCPs. The RCC-PI may request targeted follow-up data from the relevant HCP or medical facility if clarification is needed on any reported study endpoints or SAEs.

When a congenital anomaly is reported, it will be reviewed by an expert in teratology who is engaged by the RCC-PI to serve as the birth defect evaluator for this study. The birth defect evaluator's responsibilities will include the review, evaluation, and classification of all reports of birth defects.

To screen for developmental issues, the parent/legal guardian will be asked to complete the 9-, 18-, and 24-month ASQ-3 when the infant's corrected age corresponds to 9, 18, and 24 months, for example, parents/legal guardians of an infant born 3 months premature will complete the 9-month ASQ-3 at 12 months chronological age. Any child

who scores in the black zone (≥2 SD below the mean) (see Section 6.2.5.1) in any of the 5 domains of the ASQ-3 will be referred to a qualified assessor for a developmental evaluation (e.g., using the Bayley Scales of Infant Development, third edition [BSID-III]), and a neurologic examination will be conducted, if indicated. An overall assessment of delay in the areas of communication, gross and fine motor, problem-solving, and personal-social development will be rendered. As part of normal management, some infants may already have undergone a formal developmental evaluation using the BSID-III; in these cases, if testing was recent (≤3 months), the BSID-III will not be repeated and RCC-PI will request results from the relevant HCP. BSID-III retesting will be requested if the child's ASQ-3 scores are in the black zone on a subsequent ASQ-3 test following the first BSID III referral. Based on results from the ASQ-3 administered at 24 months corrected age and if no cerebral palsy diagnosis has been made to date (see Section 6.2.5.1), the infant may be referred to a qualified examiner for a formal assessment of cerebral palsy.

The M-CHAT-R/F will be completed for all infants at 18 and 24 months (corrected age) and the CBCL/1.5–5 will be completed for all infants at 24 months (corrected age) to assess the risk for other behavioral problems or autism spectrum disorder (ASD). If at any of these time points a child has an M-CHAT-R/F score that indicates further evaluation is required and/or a CBCL/1.5–5 score above the 97th percentile for a subset of prespecified questions, the child will be referred to a specialist for a formal assessment.

Protocol Amendment 2 has updated the total study duration to 24 months. Babies or infants that have passed the 24-month assessments after the amendment implementation are not required to continue further within the study, nor do they need to complete any subsequent study-related assessments. Following completion of the study, the neonates will continue their normal pediatric standard of care with their primary care pediatrician or health care provider.

The 24-month data will form the final study endpoint assessment timing; however, if data have been collected from a baby/infant after they have passed the 24-month endpoint, then this data will be included as a data listing within the clinical study report.

Data and genetic samples from the Phase III SPTL treatment studies may be used as part of a genetic analysis using data collected in this study, if relevant. No additional genetic samples are required.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 2), are essential and required for study conduct. 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.

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

3.2. Discussion of Design

Longitudinal infant outcome studies are often fraught with a high rate of loss to follow-up that can introduce ascertainment bias [Callanan, 2001; Tin, 1998]. The design of this study takes into account the operational and practical challenges involved in retaining infants, especially those who may have a diverse set of outcomes due to varying gestational age at birth. Rather than requiring visits for formal outcome interviews and assessments of the infants and children, parent/legal guardian-reported outcomes will be the first-line source of health and developmental information, and parents will record data using an eDC system to allow entry of data regardless of where it is obtained. The child's primary HCP will be asked to provide data when the parent/legal guardian reports a chronic condition, birth defect, genetic condition or syndrome; or a change in a previously reported condition. If the child's primary HCP is unable to provide the information, another relevant HCP involved with the care of the child will also be asked to provide data. All congenital anomalies will be reviewed by an expert in teratology who is engaged by the RCC-PI to serve as the birth defect evaluator.

Studies have affirmed that parents are a reliable source of information regarding their child's health and development. The validity of parental reports of infant and child hospital admissions and chronic health conditions has been shown to be high [Spencer, 2000]. Likewise, it has been demonstrated with validated tools such as the ASQ-3 that parents' observations are useful in performing developmental screening [Squires, 1998; Rydz, 2005]. Using the parents/legal guardians as first-line reporters will ensure the quality of data and enhance long-term retention in the safety follow-up. Furthermore, because parents tend to spend more time with their child than anyone else, their assessments are likely to be reliable. To guard against reporting bias, the parent/legal guardian, child's HCPs, and all study staff will be masked until completion of the follow-up study with respect to the mother/child's Phase III SPTL treatment assignment (see Section 5.3).

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

Enrollment of infants into this follow-up study will depend upon enrollment of mothers into the Phase III SPTL treatment studies. Efforts will be taken in those studies to maximize enrollment of all infants.

4.1. Number of Subjects

The sample size for this study will depend on the total number of subjects enrolled in the Phase III SPTL treatment studies.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number CM2006/00201/06].

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

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

1. Mother is randomly assigned and dosed (retosiban or comparator) in 1 of the Phase III SPTL retosiban clinical studies.
2. Infant is alive at 28 days post EDD.
3. Written informed consent is obtained from the parent(s) or legal guardian(s) of the infant. The parent/legal guardian of participants aged 12 to 17 years must also provide written agreement for the infant to participate in the study where required by applicable regulatory and country or state requirements.

4.3. Exclusion Criteria

Because this study is focused on safety and infant outcomes, all infants who meet the inclusion criteria will be eligible to enroll in the study. There are no formal exclusion criteria for participation.

4.4. Withdrawal Criteria

A child may be withdrawn from the study due to loss to follow-up or if the child's parent/legal guardian voluntarily withdraws consent. All data collected up to the time of withdrawal will be included in the analysis. If a parent/legal guardian fails to complete an assessment, but wishes to remain in the study, they will be allowed to continue by completing future assessments.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

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.

5.2. Treatment Assignment

The Phase III SPTL treatment study treatment group and strata to which mothers were assigned will be maintained during analysis of data from the child follow-up study.

5.3. Blinding

The parent/legal guardian, child, the child's HCPs, and all study personnel (from this study) will remain blinded to the treatment the mother received in the Phase III SPTL study and will remain blinded throughout the duration of this child follow-up study.

The child will be given a new subject identification number at the start of this follow-up study. The child's subject identification number from the Phase III SPTL treatment studies will be masked to maintain the blind of the follow-up study as treatment assignment will be unblinded at the conclusion of the Phase III SPTL treatment studies. The details of maintaining study blinding will be provided in the SPM.

There is no formal interim analysis planned for this study. The independent data monitoring committee (IDMC) will review unblinded data from this study along with data from any ongoing Phase III SPTL treatment study periodically in accordance with the IDMC charter. Unblinded data will be provided by an independent statistical data analysis committee.

The RCC-PI or treating physician may unblind a subject's treatment assignment in the case of an emergency OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the RCC-PI.

RCC-PIs have direct access to the subject's individual study treatment by contacting a designated PPD unblinded safety specialist via the SAE 24-Hour Safety Hotline; the designated unblinded safety specialist will perform the emergency unblinding and inform the RCC-PI of the mother's treatment assignment (refer to the SPM for details).

It is preferred (but not required) that the RCC-PI first contact the PPD medical monitor to discuss options before unblinding the subject's treatment assignment.

After the subject has been unblinded, the investigator should not reveal the treatment assignment to the PPD medical monitor unless that information is important for the safety of subjects currently enrolled in the study (refer to the SPM for details).

The date and reason for the unblinding must be fully documented in the eCRF.

This protocol will be filed to the Investigational New Drug Application of the United States. Serious AEs requiring an expedited investigational new drug safety report (blinded for investigational drug treatment) will be sent to all participating RCC-PIs. Further reporting to RCC-PIs or regulatory authorities will be performed in accordance with local regulations. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment

assignment, may be sent to RCC-PIs in accordance with local regulations and/or GSK policy.

5.4. Product Accountability

Not applicable

5.5. Treatment Compliance

Not applicable

5.6. Concomitant Medications and Nondrug Therapies

There are no restrictions regarding permitted medications or nondrug therapies. Infants will be followed and treated according to HCP standard of care.

5.7. Treatment After the End of the Study

Not applicable

5.8. Treatment of Study Treatment Overdose

Not applicable

6. STUDY ASSESSMENTS AND PROCEDURES

The child's parent/legal guardian will be the primary data reporter to the study. Confirmation of key study endpoints will be obtained from applicable HCPs or health care facilities. The infants and children will be followed beginning from after 28 days post EDD and until 24 months chronological age. Baseline characteristics and demographic data will be captured from the Phase III SPTL treatment studies and combined with child follow-up data for analyses. Refer to Table 2 for a summary of data points to be collected and the time frame for assessment.

The time points for parent-completed questionnaires are scheduled to maintain the participant's interest in study continuation and minimize losses to follow-up. Questionnaires will be associated with the child's age; in some cases, the age will be chronological and in other cases, it will be corrected for prematurity. The timing of the first questionnaire is scheduled to begin at 2 months chronological age and end at 24 months chronological age. Contingent on the infant's chronological age at the time of entry into the follow-up study, all of the questionnaires may not be completed for each participant. The SPM will provide explicit details on study procedures to ensure proper timing of questionnaires.

It is noted that as part of the Phase III SPTL treatment studies, the infant's mother will be asked to complete the Edinburgh Postnatal Depression Scale (EPDS) using the same eDC

system as will be utilized for this study. The EPDS should ideally be completed at 6 weeks (-2 weeks/+6 weeks) post-delivery but may be completed as early as 4 weeks post-delivery or as late as 12 weeks post-delivery. While the timing for EPDS may fall into the time period for this study, data will be captured as part of the Phase III SPTL treatment study, and the SPTL treatment study investigator will be responsible for reviewing information and any action required. As such, the EPDS is not reflected in Table 2. The SPM will provide details on the EPDS completion and process.

Table 2 Time and Events Table

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.

6.1. Critical Baseline Assessments

The final assessment of the Phase III SPTL treatment studies will occur at 28 days post EDD when neonatal morbidity assessments are collected. Select data from this assessment will serve as baseline data for this study, in addition to data collected from the maternal medical record and newborn medical record during the Phase III SPTL treatment studies. These data will be transferred in a blinded manner from the Phase III SPTL database to the child follow-up study database.

At Baseline, the Phase III SPTL treatment study investigator will obtain updated contact information from the parent/legal guardian; contact information will also be collected for at least 1 additional person (as described in the SPM) to minimize the number of infants and children lost to follow-up.

6.2. Safety

The focus will be on collecting the safety outcomes as defined in the objectives (e.g., hospitalization, death) and 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.

6.2.1. Morbidity and Mortality Endpoints

The main objective of the study is to characterize the clinical safety in terms of infant morbidity and mortality in infants and children exposed to retosiban or comparator during the Phase III SPTL treatment studies. The morbidity endpoints will be assessed at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age. Based on the discretion of the RCC-PI, medical records may need to be obtained from the applicable medical facility for any infants who have not yet been discharged from their birth hospitalization (see Section 6.2.1.1.1 and Section 6.3).

6.2.1.1. Parent/Legal Guardian-Completed Child Health Inventory

The child's parent/legal guardian will be asked to complete the CHI at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age. At each time point, the completion window is +6 weeks; however, CHI questionnaires completed outside the completion window will not be considered a protocol deviation.

The CHI administered at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age will screen for infant mortality and morbidity and capture data on resource utilization. To facilitate data collection, parents/legal guardians will be provided with an electronic device that will enable them to provide the protocol-required data. They will have the option to use alternative ways to access the same system (e.g., their own personal devices). Further details will be provided in the SPM.

The CHI will collect information about the child's overall health after the child has reached 28 days post EDD. The child's parent/legal guardian will be asked to relate

information from contacts with the health care system including ER/UC visits, hospitalizations, surgeries, use of special equipment, nonmedical therapy, and visits to medical specialists. Simple questions will be asked to ascertain whether chronic conditions or congenital anomalies related to the study endpoints are affecting the child's health.

At the initial completion of the CHI, the parent/legal guardian will be asked about all morbidity and mortality endpoints and, if required based on the child's age, the resource utilization endpoints. At subsequent completions of the CHI, up to 24 months chronological age, the parent/legal guardian will be asked the status of previously reported conditions (e.g., worse, better, or resolved), as appropriate. They will also be asked if any of the other morbidity and mortality endpoints and resource utilization endpoints, as required, have occurred since the last assessment.

The parent/legal guardian will be asked to record anthropometric data such as weight, length, and head circumference for the child at each well-child visit in a special electronic diary. Data from the diary will be extracted to correspond with study data collection time points (e.g., 6-month well-child visit anthropometric data will be associated with the 6-month study data collection).

6.2.1.1.1. Confirmation of Parent-Reported Data

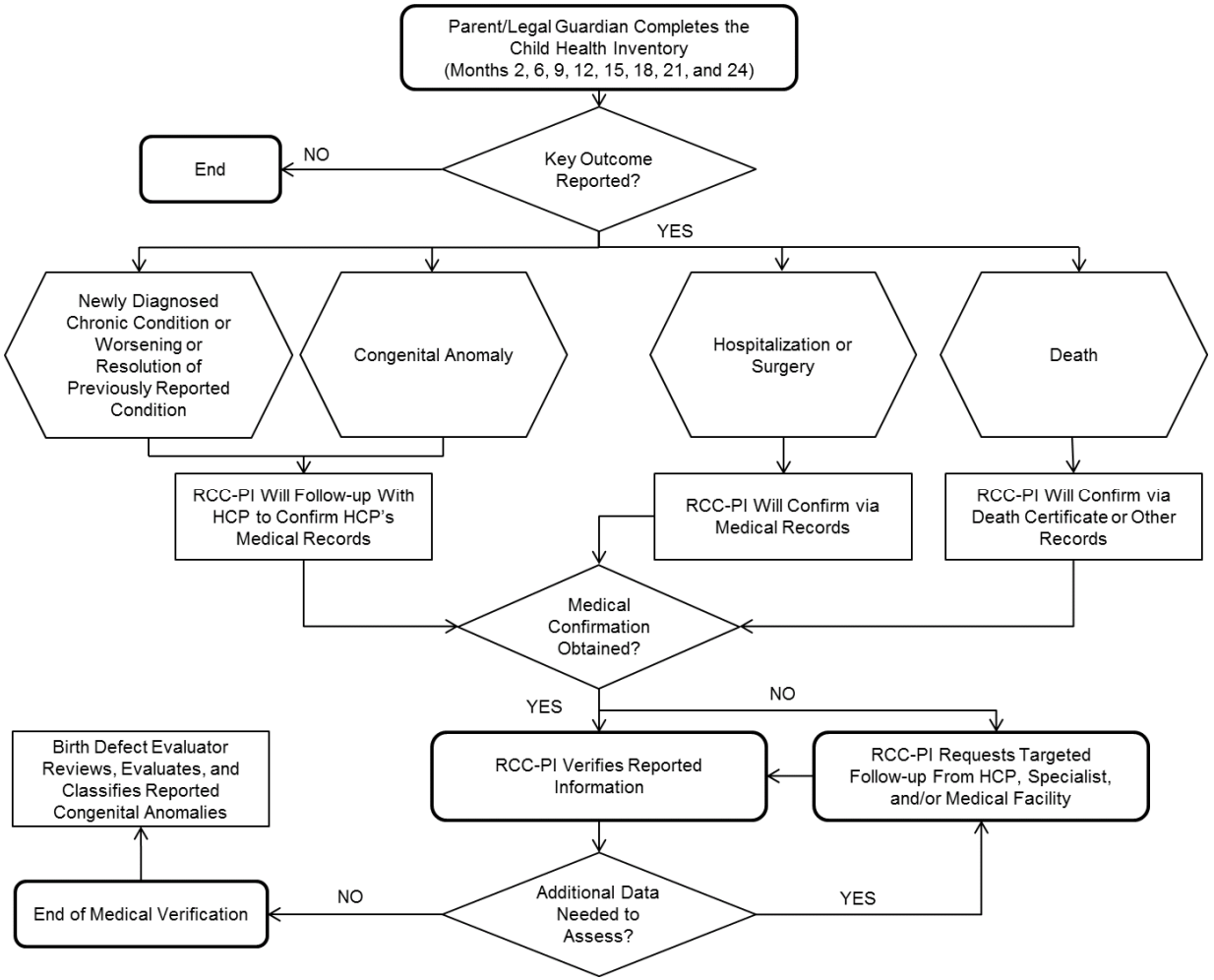
If the parent/legal guardian indicates that the child has been newly diagnosed (after 28 days post EDD) with chronic conditions or congenital anomalies via the CHI, follow-up will be undertaken via the RCC-PI with the applicable HCP to confirm the parent report. At subsequent CHIs, if the parent/legal guardian indicates that a previously reported condition has worsened or resolved, the HCP will also be asked to provide confirmation. If the condition qualifies as an SAE, additional information will be requested to assist the RCC-PI with the process of SAE reporting.

The specific process by which confirmation with HCPs and health care facilities will be obtained is presented in the SPM.

All morbidity and mortality endpoints (defined in Section 6.2) will require medical confirmation. All hospitalizations and deaths require medical confirmation by medical records or death certificate. All surgeries, except routine, simple outpatient procedures (e.g., circumcision), require confirmation by medical records. If the parent/legal guardian indicates that the child has had an ER/UC visit, the RCC-PI will use discretion and obtain medical records when the reported indication suggests a true emergency. Additional details regarding ER/UC visits will be provided in the SPM. If follow-up with the HCP is recommended, medical confirmation of the follow-up is required.

The confirmation process is iterative and may be triggered at multiple times throughout the study to provide confirmation of parent-reported conditions and events. Medical input will override parent-reported data. An overview for the collection and review of data for the CHI is provided in Figure 2.

Figure 2 Child Health Inventory: Flow Chart of Data Collection and Review



CHI = Child Health Inventory; HCP = health care provider; RCC-PI = research coordinating center-principal investigator.

1. The CHI completed at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age will screen for infant mortality and morbidity and capture data on resource utilization.

6.2.2. Chronic Medical Conditions

The proportion of infants and children with newly diagnosed (after 28 days post EDD) chronic medical conditions by type of condition will be recorded.

6.2.2.1. Respiratory Conditions

Respiratory conditions will include the following:

- Chronic lung disease newly diagnosed (after 28 days post EDD) defined as increased oxygen requirements (i.e., any increase in previously documented O_2 use, and/or a change to how the child receives supplemental O_2)
- Reactive airway disease, defined as a chronic lung condition associated with inflammation of the airways associated with wheezing and requiring episodic ongoing treatment with bronchodilators and/or inhaled or systemic steroids
- Paralyzed vocal cords, defined as impairment of the vocal cords that result in acute or chronic respiratory compromise or abnormalities in the infant's voice
- Airway obstruction

6.2.2.2. Neurological Conditions

Neurological conditions will include the following:

- Cerebral palsy, defined as a chronic, nonprogressive neurologic disorder encompassing impaired motor function affecting movement, posture, balance muscle control, coordination, tone, or reflexes.
- Seizure disorder, defined as episodic occurrence of seizure activity requiring ongoing anticonvulsant therapy
- Hydrocephalus requiring shunt, defined as abnormal accumulation of cerebrospinal fluid in the ventricles of the brain requiring permanent shunt placement to prevent irreversible neurologic sequelae
- ASD, defined as a neurodevelopmental disorder that impairs a child's ability to communicate and interact with others
- Attention deficit disorder (ADD), defined as a disorder of attention, organization, and impulse control, characterized by a persistent pattern of impulsiveness and a short attention span.
- Attention deficit disorder with hyperactivity (ADHD), defined as ADD with the addition of hyperactive behavior
- Learning difficulties, defined as a significantly reduced ability to understand new or complex information or to learn new skills
- Behavior disorders, defined as a general term to denote behavioral dysfunction that do not fall under the category of ADD or ADHD

6.2.2.3. Sensory Conditions

Sensory conditions will include the following:

- Vision
  - Vision impairment, defined as reduced visual capacity requiring corrective lenses
  - Blindness in 1 or both eyes, defined as absence of all or most vision or sees light only
- Hearing
  - Hearing impairment, defined as diminished sensitivity to sounds normally heard requiring amplification and not explained by middle ear effusion or chronic otitis media
  - Deafness in 1 or both ears, defined as complete inability to hear even with amplification
  - Hearing impaired, defined as uncorrected even with aids

6.2.2.4. Gastrointestinal Conditions

Gastrointestinal conditions will include the following:

- Gastroesophageal reflux disease, defined as reflux of gastric contents into the esophagus causing troublesome symptoms or complications and requiring ongoing treatment or surgical intervention
- Tube feeding, defined as the use of a nasogastric, orogastric, or gastrostomy tube to accomplish some or all infant feedings
- Short bowel syndrome, defined as inability to absorb enough nutrients and fluids from enteral intake to maintain good health, due to prior removal by surgery of a large section of the small intestine

6.2.2.5. Cardiovascular Conditions

Cardiovascular conditions will include the following:

- Pulmonary hypertension, defined as a chronic disorder of the pulmonary vasculature characterized by elevated pulmonary vascular resistance
- Hypertension requiring pharmacologic treatment

6.2.2.6. Renal Conditions

Renal conditions will be defined as the following:

- Renal impairment requiring dialysis

6.2.2.7. Growth Parameters

Growth parameters will include the following:

- Poor weight gain, defined as less than the third percentile on standard weight chart based on the WHO Child Growth Standards (http://www.who.int/childgrowth/standards/en/)
- Reduced length, defined as less than the third percentile on standard length chart based on the WHO Child Growth Standards (http://www.who.int/childgrowth/standards/en/)
- Reduced head circumference, defined as 2 or more standard deviations below the median based on the WHO Child Growth Standards (http://www.who.int/childgrowth/standards/en/)
- Failure to thrive as diagnosed by an HCP

6.2.3. Congenital Anomalies

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

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

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

6.2.4. Infant and Child Deaths

This study will assess the proportion of infant and child deaths that occur after 28 days post EDD and up to 24 months chronological age.

6.2.5. Parent/Legal Guardian-Completed ASQ-3, M-CHAT-R/F, and CBCL/1.5–5 and Possible Referral to a Specialist

The parent/legal guardian will be asked to complete standardized developmental screening of the infant through completion of the ASQ-3. The ASQ-3 was developed and validated to be used as a developmental screening tool; it has been used globally and translated into a number of different languages. The tool has been demonstrated to reliably and accurately identify children with delays who should receive further in-depth assessment. The ASQ-3 includes a series of questions designed to assess 5 areas of development: communication, gross motor, fine motor, problem-solving, and personal-social. The questions target behaviors that are appropriate for particular developmental milestones; there are individual ASQ-3 questionnaires for age intervals ranging from 2 to 66 months. These behaviors are easy for parents to observe, and they are asked to indicate whether or not the child can perform the behavior.

The 9-, 18-, and 24-month ASQ-3 questionnaires will be used in this study. These time points comply with recommended developmental screening assessment guidelines from the American Academy of Pediatrics [Council on Children with Disabilities, 2006]. The parent/legal guardian will be asked to complete the 9-, 18-, and 24-month ASQ-3 when the infant's corrected age corresponds to 9, 18, and 24 months, for example, parents/legal guardians of an infant born 3 months premature will complete the 9-month ASQ-3 at 12 months chronological age. To facilitate data collection, the parent/legal guardian will be provided with an electronic device that will enable them to provide the protocol-required data. They will have the option to use alternative ways to access the same system (e.g., their own personal devices). Further details will be provided in the SPM. The completion window for the ASQ-3 is +30 days at Month 9 and ±30 days at Months 18 and 24; however, questionnaires completed outside the completion window will not be considered a protocol deviation. It is essential to make age adjustments for prematurity when selecting the appropriate ASQ-3. Based on results from the ASQ-3 administered at 24 months corrected age and if no cerebral palsy diagnosis has been made to date (see Section 6.2.5.1), the infant may be referred to a qualified examiner for a formal assessment of cerebral palsy.

The M-CHAT-R/F will be completed for all infants at 18 and 24 months (corrected age) and the CBCL/1.5–5 will be completed for all infants at 24 months (corrected age) to assess the risk for other behavioral problems or ASD. If at any of these time points a child has an M-CHAT-R/F score that indicates further evaluation is required and/or a CBCL/1.5–5 score above the 97th percentile for a subset of prespecified questions, the child will be referred to a specialist for a formal assessment. An overview for the collection and review of data for the M-CHAT-R/F and CBCL/1.5–5 is provided in Figure 3.

The M-CHAT-R/F is a parent-reported autism screening tool designed to identify children 16 to 30 months of age who should receive a more thorough assessment for possible early signs of ASD or developmental delay [Robins, 2014]. The M-CHAT-R/F consists of 20 questions that are answered with either "yes" or "no." Total scores on the M-CHAT-R/F between 0 and 2 indicate a low risk, scores between 3 and 7 indicate a medium risk and triggers administration of the follow-up questionnaire, and scores between 8 and 20 indicate a high risk. In this study, infants with test scores that indicate that further evaluation is required (either after an initial medium-risk score and further follow-up or an initial high-risk score) will be considered to have possible signs of ASD or developmental delay and will be referred to a developmental specialist for a formal assessment.

The CBCL/1.5–5 is a widely used parent-completed questionnaire of the Achenbach System of Empirically Based Assessment (ASEBA). The ASEBA is based on carefully conducted empirical studies and is designed to assess, in a standardized format, behavioral problems and social competencies (Achenbach, 2001). The CBCL/1.5-5 includes approximately 100 items that describe specific kinds of behavioral, emotional, and social problems that characterize preschool children between the ages of 1.5 and 5 years. Scores on the full CBCL/1.5-5 between the 93rd and 97th percentile are in the borderline range and scores above the 97th percentile are in the significant range of clinical concern. In this study, infants with test scores above the 97th percentile for a subset of prespecified questions that relate to attention or hyperactivity problems syndrome or the American Psychiatric Association's Diagnostic and Statistical Manual (DSM)-oriented attention-deficit/hyperactivity disorder scale will be considered to have a behavior problem, which will trigger a referral to a developmental specialist for a formal assessment.

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; however, questionnaires completed outside the completion window will not be considered a protocol deviation.

For further details regarding the CBCL/1.5–5 and M-CHAT-R/F, refer to the SPM.

6.2.5.1. The ASQ-3 Score Interpretation and Possible Specialist Referral Recommendations

The ASQ-3 scores for this study will be interpreted and recommendations will be offered according to the following:

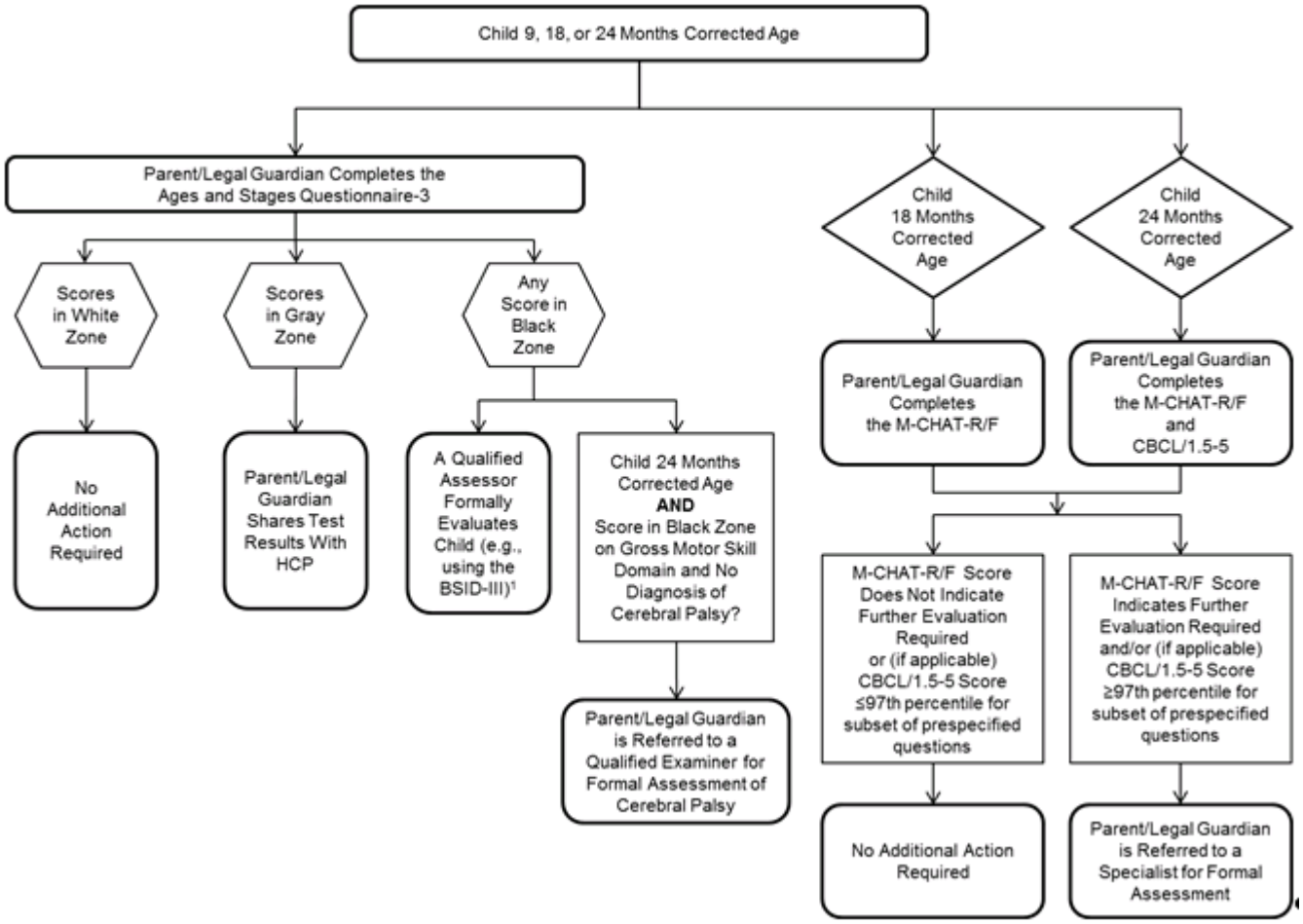
- The child's development will be considered to be on schedule if the child's ASQ-3 scores are in the white zone (higher than 1 SD below the mean), and no further action is required.
- If the child's ASQ-3 scores are in the grey zone (≤1 SD below the mean), the parent/legal guardian may share the ASQ-3 test results with the child's HCP.

- If any of the child's ASQ-3 scores are in the black zone (≥2 SD below the mean), then the child's parent/legal guardian will be asked if the child is already under the care of a developmental specialist who can or has made a formal assessment (e.g., using the BSID-III). If a recent (≤3 months) BSID-III was conducted, the BSID-III will not be repeated and the RCC-PI will request results from the relevant HCP. If the child is not currently under the care of a developmental specialist, then the parent/legal guardian will be referred to a qualified assessor for developmental evaluation (e.g., using the BSID-III), and a neurologic examination will be conducted, if indicated.
- BSID-III retesting will be performed if the child's ASQ-3 scores are in the black zone on a subsequent ASQ-3 test following the first BSID-III referral.
- If, at 24 months corrected age, the child's ASQ-3 gross motor domain score is in the black range and the child has not already been diagnosed with cerebral palsy, the parent/legal guardian will be referred to a qualified examiner for a formal assessment to determine if this condition is present.

Reports from all specialists will be included in the subject's source documents. For further details regarding the ASQ-3 refer to the SPM.

An overview for the collection and review of data for the ASQ-3 is provided in Figure 3.

Figure 3 ASQ-3, M-CHAT-R/F, and CBCL/1.5–5: Flow Chart of Data Collection and Review



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; HCP = health care provider; M-CHAT-R/F = Modified Checklist for Autism in Toddlers-Revised with Follow-Up; RCC-PI = research coordinating center-principal investigator.

1. A neurologic examination will also be conducted, if indicated.

6.2.5.2. Neurodevelopment

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.

- Proportion of infants with an ASQ-3 score in the black zone for 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 cognitive impairment (<4)
- Proportion of infants with a BSID-III score >2 SDs below the mean score for the gross motor scale (<4)
- Proportion of infants with a 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 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

6.2.6. Overall Measure of Neurodevelopmental Impairment

- 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 defined as grade 2 or 3 and severe defined as grade 4 or 5 using the Gross Motor Functional Classification System [GMFCS]) (at 24 months corrected age)

- 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

6.2.7. Adverse Events

The RCC-PI or RCC site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an SAE. Nonserious AEs will not be tracked.

The outcomes for this study may represent a number of potential adverse drug experiences or events that include but may not be limited to the following:

- Reports of child hospitalizations (see Section 6.3)
- Reports of chronic health conditions in the child (see Section 6.2.2)
- Reports of congenital anomalies in the child (see Section 6.2.3)
- Reports of child death (see Section 6.2.4)
- Reports of developmental delays in the child (see Section 6.2.5.2)
- Reports of any other SAEs in the child (see Section 6.2.7.2)

6.2.7.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

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

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

6.2.7.2. Definition of an SAE

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

a. Results in death

b. Is life threatening

   NOTE: The term "life threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other

outcomes listed in the aforementioned definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

6.2.8. Laboratory and Other Safety Assessment Abnormalities Reported as SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiograms, radiological scans, vital sign measurements), including those that worsen from Baseline, felt to be clinically significant in the medical and scientific judgment of the RCC-PI are to be recorded as SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the RCC-PI to be more severe than expected for the subject's condition, are **not** to be reported as SAEs.

6.2.9. Cardiovascular Events

The RCC-PI will be required to fill out event specific data collection tools for the following SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

This information should be recorded in the specific cardiovascular eCRF within 1 week of when the SAE(s) are first reported.

6.2.10. Death Events

The proportion of deaths that occur after 28 days post EDD and up to 24 months chronological age will be collected.

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

This information should be recorded in the specific death eCRF within 1 week of when the death is first reported.

6.2.11. Time Period and Frequency of Detecting SAEs

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

Child SAEs will be collected from after 28 days post EDD until 24 months chronological age. All SAEs will be reported to GSK/PPD within 24 hours, as indicated in Section 6.2.12.

6.2.12. Method of Detecting SAEs

Serious AEs will be primarily collected through the CHI questionnaire in an electronic device. Designated events and/or responses will be followed by the HCP as discussed in Section 6.2.7.2. Care must be taken not to introduce bias when detecting SAEs. If phone contact needs to be made with a parent/legal guardian by the RCC-PI, open-ended and nonleading verbal questioning of the subject is the preferred method to clarify reported SAEs.

6.2.13. Follow-up of SAEs

Any SAEs or AEs of special interest that were ongoing at the end of the Phase III treatment studies and any new SAEs reported during this study will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

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

Serious AEs meeting predefined criteria will be reported promptly by the RCC-PI to GSK, as described in the following table, once the RCC-PI determines that the event meets the protocol definition for that event.

	Initial Reports		Follow-Up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular or death event	Initial and follow-up reports to be completed within 1 week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s), if applicable	Initial and follow-up reports to be completed within 1 week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s), if applicable

CV = cardiovascular; SAE = serious adverse event.

The contact information for reporting SAEs is as follows:

Issue	**North America Contract**	**Latin America Contact**	**Europe/Asia Contact**
Serious Adverse Event Reporting	24-Hour Safety Hotline: PPD Safety Fax: PPD	24-Hour Safety Hotline: PPD Safety Fax: PPD	24-Hour Safety Hotline: PPD Safety Fax: PPD

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

6.2.14.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the RCC-PI to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and RCC-PIs.

The RCC-PI safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to other RCC-PIs as necessary.

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

6.2.15. Other Safety Outcomes

6.2.15.1. Laboratory Assessments

Not applicable

6.2.15.2. *Ad Hoc* Maternal Reports

It is possible that during contact with the study staff (RCC staff or RCC-PI), the mother of the child being followed in this study may report her own AEs/SAEs resultant from retosiban or comparator treatment from Phase III SPTL treatment studies in an *ad hoc* manner to the RCC study staff or the RCC-PI. The RCC-PI will be responsible for conveying such events to the Phase III SPTL treatment study investigator where the intervention was given to ensure that all safety outcomes are captured.

6.3. Health Outcomes

Resource utilization exploratory endpoints include the following:

- 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 up to 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 up to 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 up to 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.

6.3.1. Parent/Legal Guardian-Completed Productivity Questionnaire

During the 24 months of participation in the study, if the infant's parent/legal guardian reports in one of the CHI questionnaires that the child is being treated by a specialist or has had emergency department visits or hospitalizations, they will be asked to complete the productivity questionnaire. This assessment asks about the impact of the child's health problems on their ability to work and perform regular daily activities. The same tool/process as the other parent/legal guardian-reported outcomes will be used for collection of this assessment. The completion window for the productivity questionnaire is +2 weeks from the date of completion of the relevant CHI; however, questionnaires completed outside the completion window will not be considered a protocol deviation.

7. DATA MANAGEMENT

7.1. Data Handling Conventions

For this study, child data will be entered into GSK/PPD-defined eCRFs, transmitted electronically to GSK/PPD, and combined with data provided from other sources, e.g., data obtained directly from the parent/legal guardian via an electronic device provided by the sponsor, its designated vendor, or the patient's own devices using a secure and validated data system. The RCC staff will enter data provided on paper into the specifically designed eCRF pages.

Management of clinical data will be performed in accordance with applicable GSK/PPD standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug.

All eCRFs (including queries and audit trails) will be retained by GSK. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

7.1.1. Attempts to Obtain the Follow-Up Information

When follow-up data are due, the applicable reporter will be contacted and asked to provide follow-up information. Subsequent attempts, as necessary, will be made through various modes of communication. If there is still no response, a final communication will be sent indicating the case is lost to follow-up. If this communication prompts a response or the requested data are later received before the study closes, the case will be re-opened and will no longer be considered lost to follow-up. Once re-opened, any data from assessments that had not been entered at the time the participant was lost to follow-up may be collected, if appropriate. If at any point in the follow-up process the reporter indicates that the participant is lost to follow-up, no further attempts will be made.

7.1.2. Loss to Follow-Up

Children for whom follow-up information is never obtained will be considered lost to follow-up. These cases will be tallied in the applicable sections of the study reports. All other cases with some follow-up data will be analyzed up to the length of child follow-up.

7.2. Validation Procedures

The ongoing data collection from parents/legal guardians will follow a specific script to elicit information from contacts with the health care system. The child's HCP will also be contacted to provide data on the child's health and resource utilization when triggered by information from the parent/legal guardian. As indicated in the previous sections, for conditions or events that may meet SAE criteria, medical confirmation and/or medical records will be obtained to provide details of the conditions. All study data will be captured in carefully designed eCRFs specific to the study objectives.

The ASQ-3, CBCL/1.5-5, and M-CHAT-R/F questionnaires that parents/legal guardians will administer at the specific ages or time points have been validated in English and selected languages.

Ensuring that the data obtained and delivered to GSK are of high quality will be an ongoing, multistep process involving programming of edit checks for critical data variables in the data management system and visual review for completeness, logic, consistency, and accuracy. As is recommended in regulatory guidance documents, eCRFs will be carefully designed to ensure data quality and integrity.

7.2.1. Follow-Up Process for Clarification of Information

If there are discrepancies in the data, the RCC-PI will contact the appropriate HCP for clarification. Subsequent attempts will be made, if necessary. If no further information is obtained on an otherwise evaluable case, the discrepant information in the data fields may be left blank, identified as "unspecified." On a case-by-case basis, qualified study staff or the RCC-PI may make a determination regarding discrepant information (e.g., determination of partially illegible word or illogical year).

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. 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 Section 6.2) will be descriptively summarized.

No type I error adjustments are planned.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

The sample size for this study will depend on the total number of subjects enrolled in the Phase III SPTL treatment studies. In May 2017, the 2 Phase III SPTL treatment studies were terminated early due to the feasibility of recruiting the studies in a timely manner, meaning that the size of these studies was lower than originally planned. This has resulted in a greatly reduced sample size for this study.

8.2.2. Sample Size Sensitivity

Not applicable

8.2.3. Sample Size Re-Estimation

Not applicable

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

The primary population for safety assessment will be all infants whose mothers have been randomized and received retosiban or comparator in any of the Phase III treatment trials. Of these mothers, the infant safety population includes the mother/infant pairs who enrolled into the study, the mother/infant pairs who decline to consent to the study, and the mother/infant pairs whose fetus/neonates/infants died prior to the enrollment of the study. Subjects will be analyzed according to their actual treatment in case this differs from their randomized treatment.

8.3.2. Analysis Data Sets

In this study, the analysis data set is the primary population.

8.3.3. Treatment Comparisons

8.3.3.1. 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

8.3.3.2. 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

8.3.4. Interim Analysis

There is no formal interim analysis planned for this study. The IDMC will review unblinded data from this study along with data from any ongoing Phase III SPTL treatment study periodically in accordance with the IDMC charter. The unblinded periodic safety updates will be performed and delivered to the IDMC by an independent statistical data analysis committee.

In the event of early stopping of the Phase III SPTL development program due to safety and/or lack of efficacy, children will continue to be followed until they have reached 24 months chronological age.

For any subject for which the CHI questionnaire at 3, 4, and 5 years of the child's chronological age was completed prior to Amendment 2, data will be reported.

Further analysis details will be provided in the reporting and analysis plan (RAP) and/or IDMC charter.

8.3.5. Key Elements of Analysis Plan

8.3.5.1. Safety Analyses

8.3.5.1.1. Outcomes

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. The endpoints to be descriptively summarized are those described in Section 6.2. Descriptive statistics will be calculated by treatment group and by treatment group and time, where appropriate.

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

Full details of all planned analyses will be provided in the RAP.

8.3.5.1.2. Serious Adverse Events

Serious AEs as described in Section 6.2.7.2 will be coded using MedDRA and grouped by body system. Serious AEs will be summarized by treatment group as described in Section 8.3.3. Within each group, SAEs will be summarized by frequency and proportion of total subjects, by event type, and by category of body system. Separate summaries will be given for all SAEs, drug-related SAEs, and SAEs leading to withdrawal. Where appropriate, SAEs by month will be tabulated separately.

Full details of all safety analyses will be provided in either the final protocol and/or RAP.

8.3.5.2. Health Outcomes Analyses

The objective of the exploratory planned analysis is to characterize resource utilization in infants exposed to retosiban or comparator in the Phase III SPTL treatment studies. Exploratory endpoints are those described in Section 6.3. Descriptive statistics may be calculated by treatment group and by treatment group and time, where appropriate. Full details of the planned exploratory analyses will be provided in the RAP.

8.3.5.3. Genetic Analyses

Data and genetic samples from the Phase III SPTL treatment studies may be used as part of a genetic analysis using data collected in this study, if relevant. No additional genetic samples are required.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

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

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

Written informed consent must be obtained for each infant prior to participation in the study.

9.2.1. Release of Participant Medical Information

In order to collect data from the participant's HCPs, medical release forms for each clinician who will report data to the study must be completed and signed by the child's parent/legal guardian.

9.2.2. Subject Confidentiality

Each participant's identity will be known only to the third-party contractor, RCC-PIs, and relevant HCPs (e.g., pediatrician or specialist). Child identification numbers will be assigned and used to identify study participants. The dataset used in the analysis of data will contain coded participant identifiers only.

Regulatory authorities or GSK-approved auditors may inspect the study data files, which may include personal identifier information of participants.

9.3. Quality Control (Study Monitoring)

This study will be outsourced to a contract research organization (PPD), which will perform study management, clinical operations, data collection, data management, data analysis, and report authoring under the guidance of GSK.

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

PPD will monitor the study to ensure that the:

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

9.4. Quality Assurance

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

9.5. Study and RCC Site Closure

Recruitment in participating countries will begin with initiation of the Phase III SPTL treatment studies. Recruitment will continue until the Phase III SPTL treatment studies end recruitment. Follow-up will continue until each child enrolled completes the 24-month questionnaire at 24 months chronological age. For any subject that was enrolled prior to Amendment 2, those subjects who have completed the 24 months assessments will not be required to complete the CHI questionnaire at 3, 4, and 5 years of the child's chronological age. Study close-out and final reporting activities will be initiated on completion of the follow-up on the last study participant.

Upon completion or termination of the study, the PPD monitor will conduct RCC site closure activities with the RCC-PI or RCC site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK/PPD Standard Operating Procedures.

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

If any study with retosiban is suspended or terminated, GSK/PPD will promptly inform all RCC-PIs. GSK/PPD will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the RCC-PI must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the RCC-PI must maintain all RCC site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK/PPD audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant RCC site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned,

electronic); however, caution must be exercised before such action is taken. The RCC-PI must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The RCC-PI must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

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

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

9.7. Provision of Study Results to RCC-PIs, Posting of Information on Publicly Available Clinical Trials Registers and Publication

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

GSK will also provide the RCC-PI with the full summary of the study results. The RCC-PI is encouraged to share the summary results with the parent/legal guardian of the participating child, as appropriate.

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

9.8. Independent Data Monitoring Committee

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

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11. APPENDICES

11.1. Appendix 1: Protocol Changes

Protocol Amendment Number 01

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

- Extended the study duration from 24 months to 5 years. The rationale for this change was to identify any potential neurodevelopmental and behavioral disorders through annual assessments at years 3, 4, and 5, specifically autism and attention deficit hyperactivity disorder.
- Added an assessment using a modified version of the CHI questionnaire at 3, 4, and 5 years of the child's chronological age. The rationale for this change is to address US Food and Drug Administration recommendations to extend the duration of the follow-up period to 5 years. A modified CHI questionnaire will be used to collect data to identify any potential neurodevelopmental and behavioral disorders at 3, 4, and 5 years of the child's chronological age.
- Added an additional time point for the assessment of the M-CHAT-R/F at 18 months (in addition to the assessment at 24 months). The rationale for this change was to follow current recommendations from the American Academy of Pediatrics for the assessment of the M-CHAT-R/F [Council on Children with Disabilities, 2006].
- Revised criteria for assessment using the M-CHAT-R/F, which is assessed at 18 and 24 months, and CBCL/1.5-5, which is assessed at 24 months, to make these assessments mandatory for all infants, regardless of ASQ-3 results. Previous requirement for CBCL/1.5–5 and M-CHAT-R/F was limited to children with ASQ-3 nonmotor (communication, problem-solving, and/or personal-social) domain scores in the black zone at 24 months corrected age. The rationale for this change was to follow current recommendations from the American Academy of Pediatrics [Council on Children with Disabilities, 2006].
- Removed as a neurodevelopment endpoint the proportion of infants referred for an additional behavior assessment using the M-CHAT-R/F and CBCL/1.5-5. Because the CBCL/1.5-5 and M-CHAT-R/F will be assessed for all infants at specified time points, regardless of ASQ-3 results, this endpoint is no longer applicable to this study.
- Clarified that any infant SAEs and/or AEs of special interest that were unresolved at the end of the Phase III treatment studies and any new SAEs reported during this study should be followed to stabilization or resolution in those children participating in the follow-up study.

- Removed standard care tocolytic therapy as a subgroup that may be explored as part of the safety analysis. This subgroup is no longer relevant because the Phase III SPTL Study 200719 (NEWBORN-1) prohibits concomitant tocolytic treatment during study drug administration.
- Added the following subgroups that may be explored as part of the safety analysis: established progesterone use, magnesium sulphate use, and tocolytic use following study drug discontinuation. The rationale for this change was to align endpoints with those in Phase III SPTL Study 200719 (NEWBORN-1).
- Incorporated administrative changes as detailed in a Protocol Clarification Letter dated 19-Jan-2015, clarifying that there is no requirement for the investigator to discuss unblinding with the PPD medical monitor in order to rapidly unblind a child's treatment assignment if needed.
- Incorporated other administrative changes. The rationale for these changes is to ensure a clear and complete protocol for use at the RCC sites.

Specific Changes in the Text

Title Page:

Title: Follow-Up Study to Assess Long-Term Safety and Outcomes in Infants **and Children** Born to Mothers Participating in Retosiban Treatment Studies

Study Name: ARIOS

Authors (GSK): PPD

Authors (PPD): PPD

Sponsor Information Page:

Clinical Study Identifier: 200722 **(ARIOS)**

List of Abbreviations and Definitions

ADD	**attention deficit disorder**
ADHD	**attention deficit hyperactivity disorder**
ASEBA	Achenbach System of Empirically Based Assessment
ASD	**autism spectrum disorder**
. . .	
~~GSK~~	~~GlaxoSmithKline~~

Definitions

Child **Aged from 2 years to up to 12 years, per definition of the US Food and Drug Administration**

Infant **Aged from 1 month to up to 2 years, per definition of the US Food and Drug Administration**

Summary, Rationale:

One of the major advances in perinatal medicine has been the finding that antenatal corticosteroids given to women at risk of imminent preterm birth reduces the risks for neonatal mortality and morbidity. Corticosteroids now represent the standard of care for an acute antenatal intervention to improve neonatal outcomes **in the developed world** [RCOG, 2011; ACOG, 2012].

The goal of this study **(ARIOS)**, therefore, is to assess the safety and outcomes of infants **and children** who were exposed to retosiban (GSK221149) or comparator in the planned Phase III SPTL treatment studies and provide assurance that treatment is not associated with significant adverse outcomes in early childhood.

Summary, Objectives

The study objective is to assess the safety and outcomes in infants **and children** who were exposed to retosiban or comparator in the Phase III SPTL treatment studies.

Specific objectives include the following:

- To characterize the clinical safety in terms of infant morbidity and mortality in infants **and children** exposed to retosiban or comparator **in utero**
- To characterize the clinical safety in terms of neurodevelopment in infants **and children** exposed to retosiban or comparator **in utero**
- To characterize parental productivity loss related to a sick child and infant resource utilization in terms of hospital admissions, length of stay, emergency room/urgent care (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**

Summary, Study Design:

~~This~~ **ARIOS is a** long-term infant **and child** follow-up study **that** will 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. . . . The infant will be able to be consented into the study until the later date of either the date of discharge from the birth hospitalization or up to 9 months corrected age. Infants **and children** will be followed at prespecified intervals until they have reached **5 years**

chronological age ~~24 months corrected age for preterm infants (i.e., an infant born 3 months preterm will complete the final 24 month study questionnaire at 27 months chronological age) and 24 months chronological age for term infants~~. This study does not require medical interventions or study visits to an investigational site. Instead, parents or legal guardians will be prompted at certain time points to complete developmental questionnaires and other data regarding their child's health status via an electronic device. Data collected during ~~the infant~~ **this** follow-up study will be managed by a centralized research coordinating center (RCC). Regionally based pediatricians will serve as the study principal investigators (referred to as RCC-PIs) for the follow-up study. All communications the RCC-PI has with the parent/legal guardian or the ~~infant's~~ **child's** health care provider (HCP) will occur remotely; there will be no clinic visits.

The ~~infant's~~ **child's** parent/legal guardian will be asked to complete a Child Health Inventory **(CHI)** at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age **and a modified CHI at 3, 4, and 5 years of the child's chronological age**. ~~This~~ **The CHI** questionnaire **completed up to the 24-month time point** will screen for infant mortality and morbidity and will capture data on resource utilization. **At the 3-, 4-, and 5-year time points, the CHI will screen for child mortality and morbidity, including any indicators of neurodevelopmental impairment.** If the parent/legal guardian indicates that the child has been newly diagnosed (after 28 days post EDD) with chronic conditions or congenital anomalies, follow-up by the RCC-PI will be undertaken with the applicable HCP to confirm the parent report. Persistence or resolution of conditions will be determined in subsequent questionnaires after the initial report.

If the parent/legal guardian indicates that the child has had a hospital visit or surgery or that the ~~infant~~ **child** has died, the RCC-PI will confirm by obtaining medical and other records from HCPs or medical facilities, including a death certificate, if applicable. If the parent/legal guardian indicates that the child has had an ER/UC visit, the RCC-PI will use discretion and obtain medical records when the reported indication suggests a true emergency. Additional details regarding ER/UC visits will be provided in the SPM. After review of all records, the RCC-PI may request additional targeted follow-up data from the relevant HCP or medical facility if clarification is needed on any reported study endpoints or serious adverse events (SAEs).

During the first 24 months of participation in the study, ~~I~~**i**f the parent/legal guardian indicates that the infant has been treated by specialists or has had ER/UC visits or hospitalizations, he/she will be asked to complete a productivity questionnaire to evaluate loss of parental productivity.

To screen for a delay in the areas of communication, gross motor, fine motor, problem-solving, and personal-social skills, the parent/legal guardian will be asked to complete the 9-, 18-, and 24-month Ages and Stages Questionnaire-3 (ASQ-3) when the infant's corrected age corresponds to 9, 18, and 24 months, for example, parents/legal guardians of an infant born 3 months premature will complete the 9-month ASQ-3 at 12 months chronological age. Any child with a score in the black zone (≤≥2 SD below the mean) in any of the 5 domains of the ASQ-3 will be referred to a qualified assessor

for a developmental evaluation (e.g., using the Bayley Scale for Infant Development, third edition [BSID-III]), unless the child is already under the care of a specialist who has recently conducted a BSID-III evaluation. Based on results from the ASQ-3 administered at 24 months corrected age~~, parents/legal guardians may be asked to complete the Child Behavior Checklist for Ages 1.5 to 5 (CBCL/1.5–5) and the Modified Checklist for Autism in Toddlers–Revised with Follow-Up (M-CHAT-R/F) to assess the risk for other behavioral problems or autism spectrum disorder or, alternatively,~~ **and if no cerebral palsy diagnosis has been made to date**, the infant may be referred to a qualified examiner for a formal assessment of cerebral palsy.

The Modified Checklist for Autism in Toddlers–Revised with Follow-Up (M-CHAT-R/F) will be completed for all infants at 18 and 24 months (corrected age) and the Child Behavior Checklist for Ages 1.5 to 5 (CBCL/1.5–5) will be completed for all infants at 24 months (corrected age) to assess the risk for other behavioral problems or autism spectrum disorder (ASD). If at any of these time points a child has an M-CHAT-R/F score that indicates further evaluation is required and/or a CBCL/1.5–5 score at or above the 97th percentile for a subset of prespecified questions, the child will be referred to a specialist for a formal assessment.

Summary, Study Endpoints/Assessments

Morbidity and mortality endpoints:

- 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
  - Neurological conditions
  - Sensory conditions
  - Gastrointestinal conditions
  - Cardiovascular conditions
  - Renal conditions
  - Growth parameters (only up to 24 months chronological age)
- Proportion of infants **and children** with newly diagnosed (after 28 days post EDD) congenital anomalies
- Proportion of infant **and child** deaths after 28 days post EDD and until the end of the study

Neurodevelopment endpoints:

- Neurodevelopment endpoints assessed at ages 9, 18, and 24 months, corrected for prematurity:
    - 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 impairment (<70)
    - Proportion of infants with BSID-III score ~~<~~>2 SDs below the mean score for the gross motor scale (<70)
    - Proportion of infants with BSID-III score ~~<~~>2 SDs below the mean score for the fine motor scale (<70)
    - Proportion of infants with a BSID-III score ~~<~~>2 SDs below the mean score for the language scale (<70)
    - ~~Proportion of infants referred for an additional behavioral assessment using the CBCL/1.5-5 and M-CHAT-R/F~~
    - Proportion of infants with a CBCL/1.5–5 score at or 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 ~~at the end of the study~~:
    - 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)**
    - Cognitive impairment: BSID-III Cognitive Scale Score of ~~<~~>2 SDs below mean score (<70) **(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)**
- **Proportion of infants and children with at least 1 of the following indicators of neurodevelopmental impairment at the end of the study:**
    - **Hearing impaired, uncorrected even with aids**
    - **Blindness in 1 or both eyes or sees light only**
    - **Cerebral palsy (moderate and severe)**

- **Diagnosis of ASD, attention deficit disorder (ADD), or attention deficit hyperactivity disorder (ADHD)**

Resource utilization endpoints:

- 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 the end of the study**.
- 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 the end of the study**.
- Number of surgical procedures (~~by~~ **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 the end of the study**.
- 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**.

Section 1.1, Background

Preterm birth rates ranged from approximately 5% in several European countries to 18% in some African countries. In 201~~2~~**3**, ~~over~~ **nearly** 450 000 preterm births, defined as childbirth occurring before 37 completed weeks' gestation, occurred in the United States [Martin, 20~~13~~**15**].

Section 1.1.1, Previous Human Experience

Study OTA105256 was the first Phase II clinical study of retosiban in preterm labor (n=93) **[Thornton, 2015; GlaxoSmithKline Document Number CM2006/00201/03]**. The study was designed to investigate the safety and dose response of retosiban given intravenously to women with intact membranes in preterm labor between $30^{0/7}$ and $35^{6/7}$ weeks of gestation. Final results showed that intravenous retosiban treatment was associated with a significant difference in days to delivery and significant reduction in preterm births. The mean difference in days to delivery was 8.2 days relative to placebo (95% ~~confidence~~ **credible** interval ~~[CI]~~: 2.7, 13.7**4**). Median prolongation of pregnancy was 35 days in women treated with retosiban, compared with 25 days in women assigned to the placebo group. The treatment difference was consistent across gestational ages. The proportion of preterm births was 18.7% in the retosiban group and 47.2% in the

placebo group. The relative risk for preterm birth in the retosiban group was 0.38 (95% ~~CI~~ **credible** interval: 0.15, 0.81).

The emerging safety profile for retosiban appears favorable. Results from protocol specified maternal-fetal and neonatal safety assessments were absent of any concerns and were similar between the retosiban and placebo groups. Furthermore, no clinically significant disparities in AEs were noted between groups **[Thornton, 2015]**. All reported AEs, whether maternal, fetal, or neonatal, were generally consistent with those reported ~~either~~ in the Investigator's Brochure (IB) [GlaxoSmithKline ~~(GSK)~~ Document Number CM2006/00201/03]**, IB Supplement 1 [GlaxoSmithKline Document Number 2015N228508_00],** or in the study population.

Section 1.2, Rationale:

One of the major advances in perinatal medicine has been the finding that antenatal corticosteroids given to women at risk of imminent preterm birth reduces the risks for neonatal mortality and morbidity. Corticosteroids now represent the standard of care for an acute antenatal intervention to improve neonatal outcomes **in the developed world** [RCOG, 2011; ACOG, 2012].

The goal of this study **(ARIOS)**, therefore, is to assess the safety and outcomes of infants **and children** who were exposed to retosiban (GSK221149) or comparator **in utero** in the planned Phase III SPTL treatment studies and provide assurance that treatment is not associated with significant adverse outcomes in early childhood.

Section 1.3.1., Risk Assessment

This study is a follow-up safety study of infants **and children** exposed to treatment **while in utero** 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; therefore, there are no anticipated or known risks to the infants **and children** who participate in this safety study.

The intent of this study is to ensure there have been no unintended consequences to the infants **and children** from exposure to retosiban or comparator during their mother's participation in the Phase III clinical study of retosiban, specifically with respect to the following:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Fetal exposure through placental transfer	Preclinical data indicate very minimal, if any, maternal central nervous system (CNS) penetration or placental transfer of retosiban as supported by the following: • In pregnant monkeys there was no	Analysis of maternal blood and cord blood samples will be performed to test for levels of retosiban in women who deliver at an investigative center within 12 hours of the completion of study treatment infusion as part of the

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
	detectable retosiban in the cord blood when mothers were dosed up to 100 mg/kg (approximately 7 times the human exposure). However, approximately 4% of circulating drug was detected in the cord blood when mothers were dosed at 300 mg/kg (approximately 24-fold the human exposure). • Retosiban is a substrate of P-glycoprotein and breast cancer resistant protein transporters, which are thought to play a role in keeping xenobiotics out of the CNS and out of the fetal blood, thereby limiting fetal exposure to retosiban. • In reproductive toxicology studies in pregnant monkeys, there were no adverse mother and infant behavioral or locomotor effects observed that were suggestive of CNS toxicity. • In rodent neurobehavioral safety studies, there were no adverse clinical signs observed at doses up to 1000 mg/kg.	Phase III SPTL treatment studies. Surveillance for signals indicating adverse fetal or neonatal effects with in utero exposure to retosiban will be performed throughout this study. Infants exposed to retosiban in utero will be followed for ~~a miniumum of 24 months~~ **up to 5 years** in this study to assess safety and neurodevelopmental outcomes.
Neonatal exposure via breast milk	While there are no clinical data on the degree of retosiban transfer into breast milk, the available data based on physiochemical properties suggest retosiban will be excreted into breast milk if dosed close to or during the time of milk production. Given the rapid clearance of retosiban, the risk for neonatal drug exposure via breast milk appears low but could occur in the situation where the infant is fed breast milk/colostrum produced within 12 hours of treatment. Since lactogenesis is typically delayed 30 to 48 hours postpartum in mothers going to term (and is further delayed in mothers who deliver preterm), it seems unlikely that any drug would be in the plasma postpartum to transfer into the milk.	Breast milk/colostrum samples will be collected for measurement of retosiban when delivery occurs and lactation has started within 12 hours of receiving study treatment infusion as part of the Phase III SPTL treatment studies. Infants exposed to retosiban via breast milk will be followed for ~~a miniumum of 24 months~~ **up to 5 years** in this study to assess safety and neurodevelopmental outcomes.

SPTL = spontaneous preterm labor.

Section 1.3.2., Benefit Assessment

Given the inverse relationship between the risks for prematurity complications and gestational age at birth, the development of a treatment that significantly prolongs pregnancy in women with SPTL would be invaluable if associated with improved perinatal outcomes. Results from the Phase II study OTA105256 offer hope that retosiban may prolong pregnancy to such a degree that perinatal outcomes could be favorably affected **[Thornton, 2015]**. There are currently no safety findings that would preclude further development of retosiban for an indication for the treatment of SPTL in conjunction with standard of care treatments in women with an uncomplicated, singleton pregnancy.

The benefit to infants **and children** participating in this study is the focus on following morbidity and neurodevelopment for ~~a miniumum of 24 months~~ **up to 5 years** following exposure to retosiban or comparator medication. Participating infants and children will have the benefit of access to developmental screening (Ages and Stages Questionnaire-3 [ASQ-3], Child Behavior Checklist for Ages 1.5 to 5 [CBCL/1.5–5], and the Modified Checklist for Autism in Toddlers–Revised with Follow-Up [M-CHAT-R/F]), which may not be routinely provided and will allow parents/legal guardians to monitor and track the ~~infant's~~ **child's** developmental milestones in a formalized manner. In addition, screening results may be shared with the ~~infant's~~ **child's** physician (health care providers [HCPs] or other) as requested by the parent/legal guardian. In the event a potential issue is identified and further follow-up is warranted, the ~~infant~~ **child** will be referred to developmental specialists/qualified assessors for further evaluations as part of this study. In this manner, neurodevelopmental issues may be identified earlier than would have been normally.

Section 1.3.3., Overall Benefit:Risk Conclusion

For detailed information on the identified risks and benefit:risk assessment of retosiban, refer to the IB **and IB Supplement 1** [GlaxoSmithKline Document Number CM2006/00201/03**; GlaxoSmithKline Document Number 2015N228508_00**]. The overall benefit:risk assessment of retosiban appears favorable for the mother and fetus/infant. Although, experience in pregnant women is limited, no clinical or preclinical safety issues have been identified that preclude further development.

Section 2, Objectives

The study objective is to assess the safety and outcomes in infants **and children** who were exposed to retosiban or comparator in the Phase III SPTL treatment studies. Table 1 summarizes the specific study objectives and the corresponding endpoints, which are described in detail in Section 6.2 (Safety) and Section 6.3 (Health Outcomes).

Objective	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 **(only up to 24 months chronological age)**
	  ○ 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 ~~neonatal and~~ infant **and child** deaths that occur after 28 days post EDD and until the end of the study

Objective	Endpoints

To characterize the clinical safety in terms of neurodevelopment in infants **and children** exposed to retosiban or comparator **in utero**	• 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 (<70)
	  • Proportion of infants with BSID-III score **<>**2 SDs below the mean score for the gross motor scale (<70)
	  • Proportion of infants with BSID-III score **<>**2 SDs below the mean score for the fine motor scale (<70)
	  • Proportion of infants with a BSID-III score **<>**2 SDs below the mean score for the language scale (<70)
	  ~~• Proportion of infants referred for an additional behavioral assessment using the CBCL/1.5-5 and M-CHAT-R/F~~
	  • Proportion of infants with a CBCL/1.5-5 score at or 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 ~~at the end of the study~~:
	  • 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)**
	  • Cognitive impairment: BSID-III Cognitive Scale Score of <>2 SDs below mean score (<70) **(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)**

Objective	Endpoints

	• **Proportion of infants and children with at least 1 of the following indicators of neurodevelopmental impairment at the end of the study:**
	  • **Hearing impaired, uncorrected even with aids**
	  • **Blindness in 1 or both eyes, or sees light only**
	  • **Cerebral palsy (moderate and severe)**
	  • **Diagnosis of ASD, ADD, or ADHD**

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 the end of the study. • 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 the end of the study. • Number of surgical procedures (~~by~~ **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 the end of the study. • 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**.

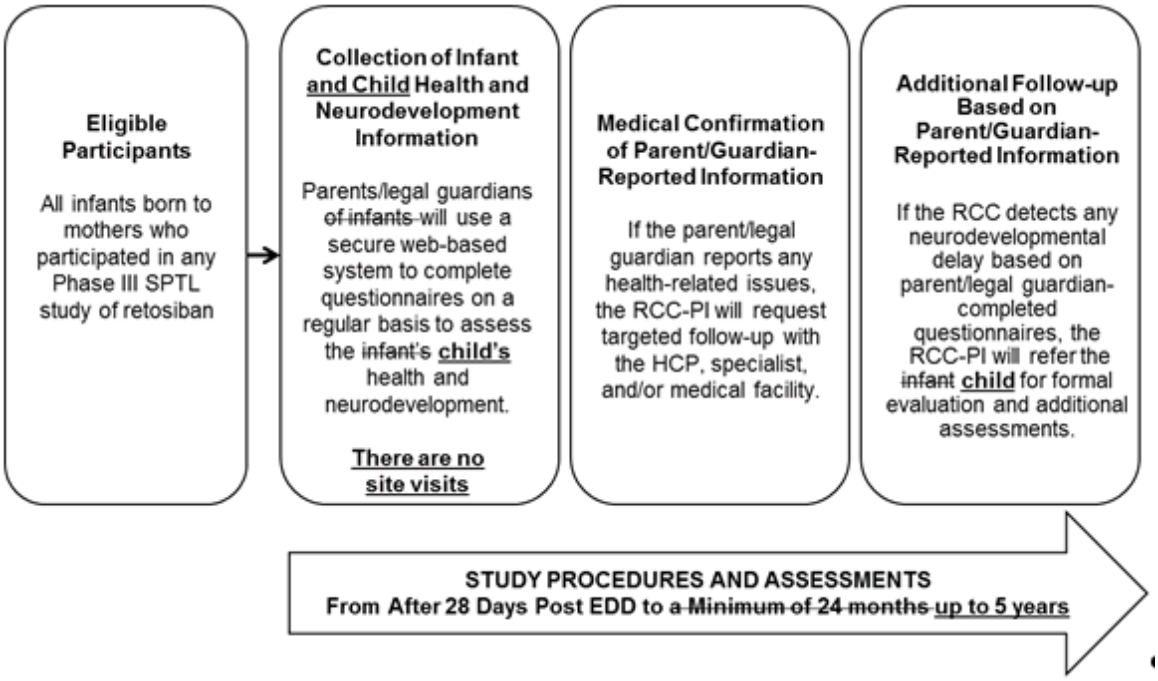
ADD = attention deficit disorder; ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; ASQ-3 = Ages and Stages Questionnaire-3; BSID-III = Bayley Scales of Infant Development, third edition; CBCL/1.5-5 = Child Behavior Checklist for Ages 1.5 to 5; EDD = estimated date of delivery; 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.

Section 3.1., Study Design

~~This~~ **ARIOS is a** long-term infant **and child** follow-up study **that** will 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. . . . The infant will be able to be consented into the study until the later date of either the date of discharge from the birth hospitalization or up to 9 months corrected age. Infants will be followed at prespecified intervals until they have reached **5 years** chronological age ~~24 months corrected age for preterm infants (i.e., an infant born 3 months preterm will complete the final 24 month study questionnaire at 27 months chronological age) and 24 months chronological age for term infants~~. . . . Infants **and children** will be followed

at prespecified intervals until they reach 5 years chronological age (see Table 2). This study does not require medical interventions or study visits to an investigational site. Instead, 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. Data collected during ~~the infant~~ **this** follow up study will be managed by a centralized RCC. Regionally based pediatricians will serve as study principal investigators (referred to as RCC-PIs) for this study. All communications the RCC-PI has with the parent/legal guardian or the ~~infant's~~ **child's** HCP will occur remotely; there will be no clinic visits. An overview of the study design is shown in Figure 1.

Figure 1, Study Design



Electronic data capture (eDC) tools and processes including electronic case report forms (eCRF) and electronic patient-reported outcome devices will allow entry of data, regardless of when it is obtained. If at any time the data suggest any developmental delay ~~of an infant~~, the RCC-PI will refer the ~~infant~~ child to a specialist (if not already under the care of a specialist) for formal evaluation and additional assessments. The ~~infant's~~ **child's** local primary care pediatric provider will be asked to provide routinely available data on the ~~infant~~ **child** to the RCC. Additional contacts may occur at the discretion of the RCC personnel to complete the data collection.

The ~~infant's~~ **child** parent/legal guardian will be asked to complete the CHI at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age **and a modified CHI at 3, 4, and 5 years of the child's chronological age**. The **CHI** questionnaire **completed up to the 24-month time point** will screen for infant mortality and morbidity and will capture data on resource utilization. **At the 3-, 4-, and 5-year time points, the CHI will screen for child mortality and morbidity, including any indicators of neurodevelopmental impairment.** If the parent/legal guardian indicates that the child has been newly diagnosed (after 28 days post EDD) with chronic conditions or congenital anomalies

follow up will be undertaken with the applicable HCP to confirm the parent/legal guardian report. Persistence or resolution of conditions will be determined in subsequent questionnaires after the initial report. If protocol specific evaluations are in progress at the end of the child's protocol defined participation in this study (~~24 months corrected age for preterm infants or 24 months~~ **5 years** chronological age ~~for term infants~~) and results have not yet been received or reported, the time period may be extended to collect those reports.

If the parent/legal guardian indicates that the child has had any emergency room/urgent care (ER/UC) visits, he/she will be asked to record the number of visits and to indicate if the visit resulted in hospitalization. If the parent/legal guardian indicates that the ~~infant~~ **child** has been hospitalized or has had any surgeries, medical records from the applicable medical facility will be obtained and abstracted for pertinent details, including principal and secondary discharge diagnoses, type of hospital unit admitted to (e.g., neonatal intensive care unit [NICU], Pediatrics, pediatric intensive care unit [PICU], Nursery level 3, ICU), and length of stay. If the parent/legal guardian indicates that the ~~infant~~ **child** died after 28 days post EDD, details of the death will be obtained from the death certificate or appropriate HCP or medical records if the death certificate is not available. Note that all infant deaths that occur before 28 days post EDD will be captured and reported as part of the Phase III SPTL treatment studies.

During the first 24 months of participation in the study, ~~I~~if the parent/legal guardian indicates that the infant has been treated by specialists or has had ER/UC visits or hospitalizations, he/she will be asked to complete a productivity questionnaire to evaluate loss of parental productivity.

To screen for developmental issues, the parent/legal guardian will be asked to complete the 9-, 18-, and 24-month ASQ-3 when the infant's corrected age corresponds to 9, 18, and 24 months, for example, parents/legal guardians of an infant born 3 months premature will complete the 9-month ASQ-3 at 12 months chronological age. Any child who scores in the black zone (~~≤~~≥2 SD below the mean) (see Section 6.2.5.1) in any of the 5 domains of the ASQ-3 will be referred to a qualified assessor for a developmental evaluation (e.g., using the Bayley Scales of Infant Development, third edition [BSID-III]), and a neurologic examination will be conducted, if indicated. An overall assessment of delay in the areas of communication, gross and fine motor, problem-solving, and personal-social development will be rendered. As part of normal management, some infants may already have undergone a formal developmental evaluation using the BSID-III; in these cases, if testing was recent (≤3 months), the BSID-III will not be repeated and RCC-PI will request results from the relevant HCP. BSID-III retesting will be requested if the child's ASQ-3 scores are in the black zone on a subsequent ASQ-3 test following the first BSID III referral. Based on results from the ASQ-3 administered at 24 months corrected age~~, parents/legal guardians may be asked to complete the Child Behavior Checklist for Ages 1.5 to 5 (CBCL/1.5–5) and the Modified Checklist for Autism in Toddlers–Revised with Follow-Up (M-CHAT-R/F) to assess the risk for other behavioral problems or autism spectrum disorder or, alternatively,~~ **and if no cerebral palsy diagnosis has been made to date**, the infant may be referred to a qualified examiner for a formal assessment of cerebral palsy.

The Modified Checklist for Autism in Toddlers–Revised with Follow-Up (M-CHAT-R/F) will be completed for all infants at 18 and 24 months (corrected age) and the Child Behavior Checklist for Ages 1.5 to 5 (CBCL/1.5–5) will be completed for all infants at 24 months (corrected age) to assess the risk for other behavioral problems or autism spectrum disorder (ASD). If at any of these time points a child has an M-CHAT-R/F score that indicates further evaluation is required and/or a CBCL/1.5–5 score at or above the 97th percentile for a subset of prespecified questions, the child will be referred to a specialist for a formal assessment.

Section 3.2., Discussion of Design

Longitudinal infant outcome studies are often fraught with a high rate of loss to follow up that can introduce ascertainment bias [Callanan, 2001; Tin, 1998]. The design of this study takes into account the operational and practical challenges involved in retaining infants, especially those who may have a diverse set of outcomes due to varying gestational age at birth. Rather than requiring visits for formal outcome interviews and assessments of the infants **and children**, parent/legal guardian-reported outcomes will be the first-line source of health and developmental information, and parents will record data using an eDC system to allow entry of data regardless of where it is obtained. The child's primary HCP will be asked to provide data when the parent/legal guardian reports a chronic condition, birth defect, genetic condition or syndrome; or a change in a previously reported condition. If the child's primary HCP is unable to provide the information, another relevant HCP involved with the care of the ~~infant~~ **child** will also be asked to provide data. All congenital anomalies will be reviewed by an expert in teratology who is engaged by the RCC-PI to serve as the birth defect evaluator.

Studies have affirmed that parents are a reliable source of information regarding their ~~infant's~~ **child's** health and development. The validity of parental reports of infant **and child** hospital admissions and chronic health conditions has been shown to be high [Spencer, 2000]. Likewise, it has been demonstrated with validated tools such as the ASQ-3 that parents' observations are useful in performing developmental screening [Squires, 1998; Rydz, 2005]. Using the parents/legal guardians as first-line reporters will ensure the quality of data and enhance long-term retention in the safety follow-up. Furthermore, because parents tend to spend more time with their ~~infants~~ **child** than anyone else, their assessments are likely to be reliable. To guard against reporting bias, the parent/legal guardian, ~~infant's~~ **child's** HCPs, and all study staff will be masked until completion of the follow-up study with respect to the mother/~~infant's~~ **child's** Phase III SPTL treatment assignment (see Section 5.3).

Section 4.2, Inclusion Criteria

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

Section 4.4., Withdrawal Criteria

A~~n infants~~ **child** may be withdrawn from the study due to loss to follow-up or if the ~~infant's~~ **child's** parent/legal guardian voluntarily withdraws consent. All data collected up to the time of withdrawal will be included in the analysis. If a parent/legal guardian fails to complete an assessment, but wishes to remain in the study, they will be allowed to continue by completing future assessments.

Section 5.1., Investigational Product and Other Study Treatment

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.

Section 5.2., Treatment Assignment

The Phase III SPTL treatment study treatment group and strata to which mothers were assigned will be maintained during analysis of data from the ~~infant~~ **child** follow-up study.

Section 5.3, Blinding

The parent/legal guardian, ~~infant~~ **child**, the ~~infant's~~ **child's** HCPs, and all study personnel (from this study) will remain blinded to the treatment the mother received in the Phase III SPTL study and will remain blinded throughout the duration of this ~~infant~~ **child** follow-up study.

The ~~infant~~ **child** will be given a new subject identification number at the start of this follow-up study. The ~~infant's~~ **child's** subject identification number from the Phase III SPTL treatment.

The RCC-PI **or treating physician** may unblind ~~an infant's~~ **a subject's** treatment assignment ~~only~~ in the case of an emergency **OR in the event of a serious medical condition** when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject **as judged by the RCC-PI**.

~~The RCC-PI must first discuss options with GSK/PPD medical monitor or appropriate GSK/PPD study personnel before unblinding the infant's treatment assignment. The PPD unblinded medical monitor will authorize the unblinding, and the treatment assignment will be provided. The date and reason for the unblinding must be recorded in the appropriate data collection tool.~~

~~GSK's Global Clinical Safety and Pharmacovigilance department may unblind the treatment assignment for any infant with an SAE. The PPD medical monitor may unblind the treatment assignment after discussing the rationale for unblinding with the RCC-PI. Notification of unblinding will be sent to GSK, PPD, and the RCC site.~~

~~This protocol will be filed to the Investigational New Drug Application of the United States. Serious AEs requiring an expedited investigational new drug safety report (blinded for investigational drug treatment) will be sent to all participating RCC-PIs. Further reporting to RCC-PIs or regulatory authorities will be performed in accordance with local regulations. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to RCC-PIs in accordance with local regulations and/or GSK policy.~~

RCC-PIs have direct access to the subject's individual study treatment by contacting a designated PPD unblinded safety specialist via the SAE 24-Hour Safety Hotline; the designated unblinded safety specialist will perform the emergency unblinding and inform the RCC-PI of the mother's treatment assignment (refer to the SPM for details).

It is preferred (but not required) that the RCC-PI first contact the PPD medical monitor to discuss options before unblinding the subject's treatment assignment.

After the subject has been unblinded, the investigator should not reveal the treatment assignment to the PPD medical monitor unless that information is important for the safety of subjects currently enrolled in the study (refer to the SPM for details).

The date and reason for the unblinding must be fully documented in the eCRF.

Section 6, Study Assessments and Procedures

The ~~infant's~~ **child's** parent/legal guardian will be the primary data reporter to the study. Confirmation of key study endpoints will be obtained from applicable HCPs or health care facilities. The infants **and children** will be followed beginning from after 28 days post EDD and until ~~24 months corrected age (for preterm infants) or 24 months~~ **5 years** chronological age ~~(for term infants)~~. Baseline characteristics and demographic data will be captured from the Phase III SPTL treatment studies and combined with ~~infant~~ **child** follow-up data for analyses. Refer to Table 2 for a summary of data points to be collected and the time frame for assessment.

The time points for parent-completed questionnaires are scheduled to maintain the participant's interest in study continuation and minimize losses to follow up. Questionnaires will be associated with the ~~infant's~~ **child's** age; in some cases the age will be chronological and in other cases, it will be corrected for prematurity. The timing of the first questionnaire is scheduled to begin at 2 months chronological age and end at ~~24 months corrected age (for preterm infants) or 24 months~~ **5 years** chronological age ~~(for term infants)~~. Contingent on the infant's chronological age at the time of entry into the follow up study, all of the questionnaires may not be completed for each participant. The SPM will provide explicit details on study procedures to ensure proper timing of questionnaires.

Table 2 Time and Events Table

Event	28 Days Post EDD	Months								Years[1]		
		2	6	9	12	15	18	21	24	3	4	5
Written informed consent[1~~2~~]	←	—	—	—	→							
Baseline characteristics and demographic data	X[2~~3~~]											
RCC confirms and updates contact information from the parent/legal guardian	X											
Parent/legal guardian completes CHI[3~~4~~]		X	X	X	X	X	X	X	X	X[3~~4~~]	X[3~~4~~]	X[3~~4~~]
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~~5~~]		→										
Parent/legal guardian completes ASQ-3[5~~6~~]				X[5~~6~~]			X[5~~6~~]		X[5~~6~~]			
RCC-PI reviews ASQ-3 results and refers for developmental evaluation based on results[6~~7~~]				→								
Parent/legal guardian completes M-CHAT-R/F[7~~8~~]							X		X			
Parent/legal guardian completes CBCL/1.5–5[7~~8~~]									X			
RCC-PI refers child to specialist for cerebral palsy assessment (if required)[8~~9~~]									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. **Assessments performed at years 3, 4, and 5 are based on the child's chronological age.**
2. ~~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).
3. ~~2~~ Captured in Phase III SPTL treatment studies and combined with ~~infant~~ **child** follow-up data for analyses.
4. ~~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. A modified CHI will be completed at 3, 4, and 5 years of the child's chronological age. At each time point, the completion window of the CHI is +6 weeks.

~~4~~**5.** 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~~**6.** 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~~**7.** If the parent/legal guardian receives a referral, then a qualified specialist will complete required assessments.

~~7~~**8.** The CBCL/1.5–5 and M-CHAT-R/F questionnaires will ~~only~~ be completed for **all** infants ~~who score in the black zone on the 24 month corrected age ASQ-3 in any of the following domains: communication, problem solving, or personal social scale~~. 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~~**9.** 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.

Section 6.1., Critical Baseline Assessments

The final assessment of the Phase III SPTL treatment studies will occur at 28 days post EDD when neonatal morbidity assessments are collected. Select data from this assessment will serve as baseline data for this study, in addition to data collected from the maternal medical record and newborn medical record during the Phase III SPTL treatment studies. These data will be transferred in a blinded manner from the Phase III SPTL database to the ~~infant~~ **child** follow-up study database.

At Baseline, the Phase III SPTL treatment study investigator will obtain updated contact information from the parent/legal guardian; contact information will also be collected for at least 1 additional person (as described in the SPM) to minimize the number of infants **and children** lost to follow-up.

Section 6.2.1., Morbidity and Mortality Endpoints

The main objective of the study is to characterize the clinical safety in terms of infant morbidity and mortality in infants **and children** exposed to retosiban or comparator during the Phase III SPTL treatment studies. The morbidity endpoints will be assessed at 2, 6, 9, 12, 15, 18, 21, and 24 months **and 3, 4, and 5 years of the child's chronological age**. Based on the discretion of the RCC-PI, medical records may need to be obtained from the applicable medical facility for any infants who have not yet been discharged from their birth hospitalization (see Section 6.2.1.1.1 and Section 6.3).

Section 6.2.1.1., Parent/Legal Guardian-Completed Child Health Inventory

The child's parent/legal guardian will be asked to complete the CHI at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age **and a modified CHI at 3, 4, and 5 years of the child's chronological age**. At each time point, the completion window is +6 weeks; however, CHI questionnaires completed outside the completion window will not be considered a protocol deviation.

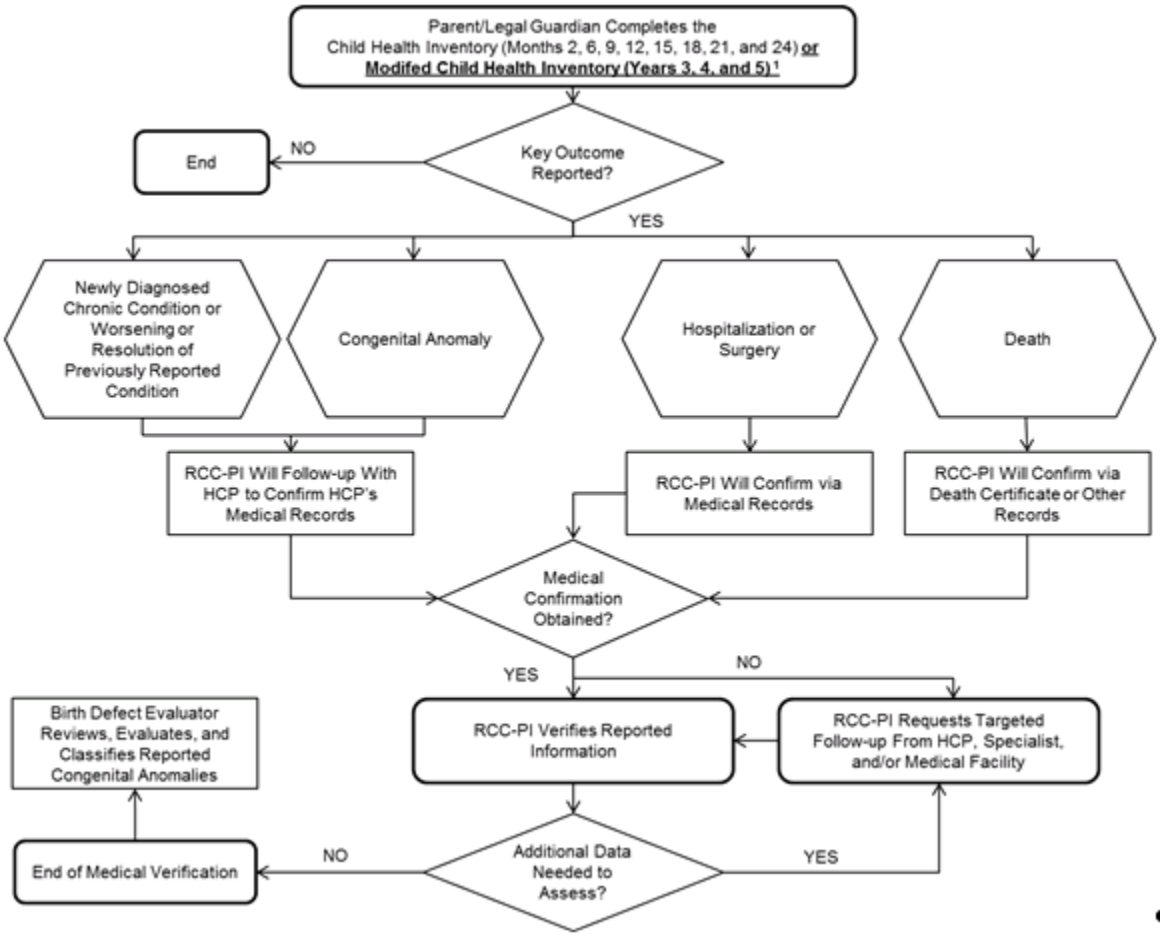
The CHI ~~will be~~ administered **at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age** will ~~to~~ screen for infant mortality and morbidity and ~~to~~ capture data on resource utilization. **At 3, 4, and 5 years of the child's chronological age, the CHI will screen for child mortality and morbidity, including any indicators of neurodevelopmental impairment.** To facilitate data collection, parents/legal guardians will be provided with an electronic device that will enable them to provide the protocol required data. They will have the option to use alternative ways to access the same system (e.g., their own personal devices). Further details will be provided in the SPM.

. . .

At the initial completion of the CHI, the parent/legal guardian will be asked about all morbidity and mortality endpoints and**, if required based on the child's age,** the resource utilization endpoints. At subsequent completions of the CHI**, up to 24 months chronological age,** the parent/legal guardian will be asked the status of previously reported conditions (e.g., worse, better, or resolved), as appropriate. They will also be

asked if any of the other morbidity and mortality endpoints and resource utilization endpoints**, as required,** have occurred since the last assessment.

Figure 2 Child Health Inventory: Flow Chart of Data Collection and Review



HCP = health care provider; RCC-PI = research coordinating center-principal investigator.

1. **The CHI completed at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age will screen for infant mortality and morbidity and capture data on resource utilization. At 3, 4, and 5 years of the child's chronological age, the CHI will screen for child mortality and morbidity, including any indicators of neurodevelopmental impairment**.

Section 6.2.2., Chronic Medical Conditions

The proportion of infants **and children** with newly diagnosed (after 28 days post EDD) chronic medical conditions by type of condition will be recorded.

Section 6.2.2.1., Respiratory Conditions

Respiratory conditions will include the following:

- Chronic lung disease newly diagnosed (after 28 days post EDD) defined as increased oxygen requirements (i.e., any increase in previously documented O_2 use, and/or a change to how the child receives supplemental O_2)
- Reactive airway disease, defined as a chronic lung condition associated with inflammation of the airways associated with wheezing and requiring episodic ongoing treatment with bronchodilators and/or inhaled or systemic steroids
- Paralyzed vocal cords, defined as impairment of the vocal cords that result in acute or chronic respiratory compromise or abnormalities in the infant's voice
- Airway obstruction

Section 6.2.2.2., Neurological Conditions

Neurological conditions will include the following:

- Cerebral palsy, defined as a chronic, nonprogressive neurologic disorder encompassing impaired motor function affecting movement, posture, balance muscle control, coordination, tone, or reflexes.
- Seizure disorder, defined as episodic occurrence of seizure activity requiring ongoing anticonvulsant therapy
- Hydrocephalus requiring shunt, defined as abnormal accumulation of cerebrospinal fluid in the ventricles of the brain requiring permanent shunt placement to prevent irreversible neurologic sequelae
- **ASD, defined as a neurodevelopmental disorder that impairs a child's ability to communicate and interact with others**
- **Attention deficit disorder (ADD), defined as a disorder of attention, organization, and impulse control, characterized by a persistent pattern of impulsiveness and a short attention span.**
- **Attention deficit disorder with hyperactivity (ADHD), defined as ADD with the addition of hyperactive behavior**
- **Learning difficulties, defined as a significantly reduced ability to understand new or complex information or to learn new skills**
- **Behavior disorders, defined as a general term to denote behavioral dysfunction that do not fall under the category of ADD or ADHD**

Section 6.2.2.7. Growth Parameters

Growth parameters will **be assessed only up to 24 months chronological age and will** include the following:

Section 6.2.3., Congenital Anomalies

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

Section 6.2.4., ~~Neonatal and~~ Infant and Child Deaths

This study will assess the proportion of ~~neonatal and~~ infant **and child** deaths that occur after 28 days post EDD and up to ~~24 months corrected age for preterm infants and 24 months~~ **5 years** chronological age ~~for term infants~~.

Section 6.2.5., Parent/Legal Guardian-Completed ASQ-3**, M-CHAT-R/F, and CBCL/1.5–5** and Possible Referral to a Specialist

The 9-, 18-, and 24-month ASQ-3 questionnaires will be used in this study. These time points comply with recommended developmental screening assessment guidelines from the American Academy of Pediatrics [Council on Children with Disabilities, 2006]. The parent/legal guardian will be asked to complete the 9-, 18-, and 24-month ASQ-3 when the infant's corrected age corresponds to 9, 18, and 24 months, for example, parents/legal guardians of an infant born 3 months premature will complete the 9-month ASQ-3 at 12 months chronological age. To facilitate data collection, the parent/legal guardian will be provided with an electronic device that will enable them to provide the protocol required data. They will have the option to use alternative ways to access the same system (e.g., their own personal devices). Further details will be provided in the SPM. The completion window for the ASQ-3 is +30 days at Month 9 and ±30 days at Months 18 and 24; however, questionnaires completed outside the completion window will not be considered a protocol deviation. It is essential to make age adjustments for prematurity when selecting the appropriate ASQ-3. Based on results from the ASQ-3 administered at 24 months corrected age **and if no cerebral palsy diagnosis has been made to date** (see Section 6.2.5.1) ~~parents/legal guardians may be asked to complete the CBCL/1.5–5 and the M-CHAT-R/F to assess the risk for other behavioral problems or autism spectrum disorder or, alternatively~~, the infant may be referred to a qualified examiner for a formal assessment of cerebral palsy.

The M-CHAT-R/F will be completed for all infants at 18 and 24 months (corrected age) and the CBCL/1.5–5 will be completed for all infants at 24 months (corrected

age) to assess the risk for other behavioral problems or ASD. If at any of these time points a child has an M-CHAT-R/F score that indicates further evaluation is required and/or a CBCL/1.5–5 score at or above the 97th percentile for a subset of prespecified questions, the child will be referred to a specialist for a formal assessment. An overview for the collection and review of data for the M-CHAT-R/F and CBCL/1.5–5 is provided in Figure 3.

The completion window for the CBCL/1/5-5 and M-CHAT-R/F is +**6 week at 18 months (M-CHAT-R/F) and** +12 weeks **at 24 months**; however, questionnaires completed outside the completion window will not be considered a protocol deviation.

For further details regarding the CBCL/1.5–5 and M-CHAT-R/F, refer to the SPM.

Section 6.2.5.1., The ASQ-3 Score Interpretation and Possible Specialist Referral Recommendations ~~and Completion of CBCL/1.5-5 and M-CHAT-R/F~~

The ASQ-3 scores for this study will be interpreted and recommendations will be offered according to the following:

- The child's development will be considered to be on schedule if the child's ASQ-3 scores are in the white zone (higher than 1 SD below the mean), and no further action is required.
- If the child's ASQ-3 scores are in the grey zone (≤1 SD below the mean), the parent/legal guardian may share the ASQ-3 test results with the child's HCP.
- If any of the child's ASQ-3 scores are in the black zone (~~≤~~≥2 SD below the mean), then the child's parent/legal guardian will be asked if the child is already under the care of a developmental specialist who can or has made a formal assessment (e.g., using the BSID-III). If a recent (≤3 months) BSID-III was conducted, the BSID-III will not be repeated and the RCC-PI will request results from the relevant HCP. If the child is not currently under the care of a developmental specialist, then the parent/legal guardian will be referred to a qualified assessor for developmental evaluation (e.g., using the BSID-III), and a neurologic examination will be conducted, if indicated.
- BSID-III retesting will be performed if the child's ASQ-3 scores are in the black zone on a subsequent ASQ 3 test following the first BSID-III referral.
- ~~If, at 24 months corrected age, the child's ASQ-3 nonmotor (communication, problem solving, and/or personal-social) domain scores are in the black zone, the parent/legal guardian will be asked to fill out the CBCL/1.5–5 and M-CHAT-R/F questionnaires. If the results of either assessment indicate an increased risk for other behavioral problems or autism spectrum disorder, the parent/legal guardian will be referred to a developmental specialist for a more formal behavioral assessment.~~
- If, at 24 months corrected age, the child's ASQ-3 gross motor domain score is in the black range and the child has not already been diagnosed with cerebral palsy,

the parent/legal guardian will be referred to a qualified examiner for a formal assessment to determine if this condition is present.

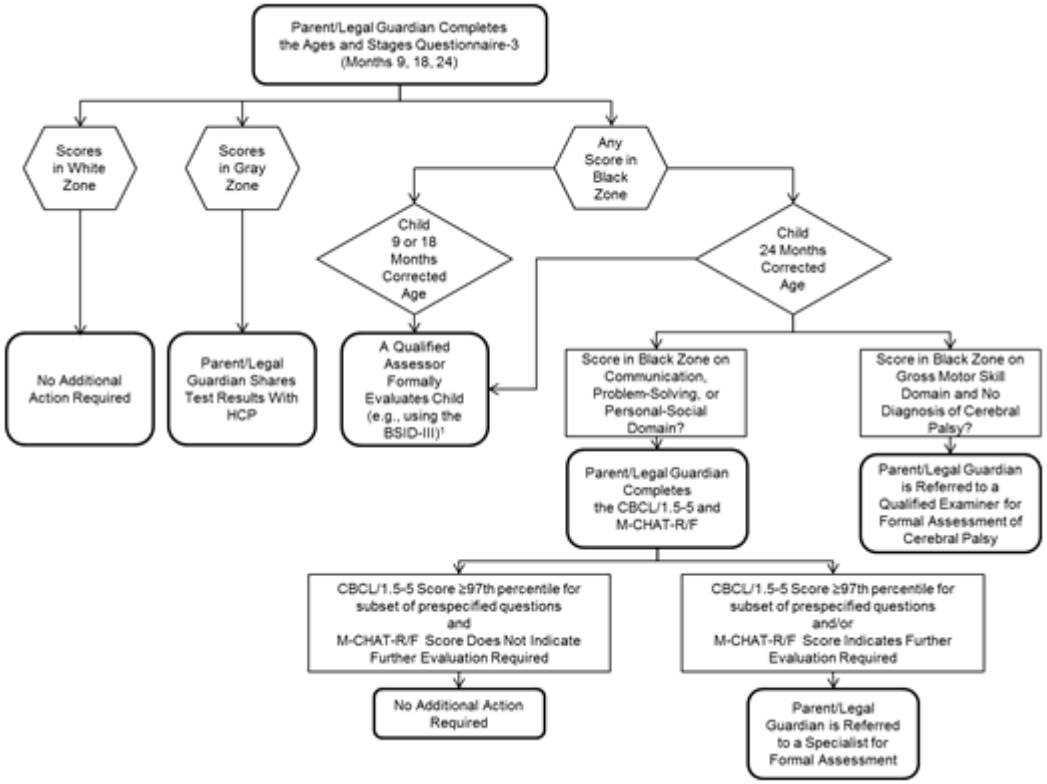
Reports from all specialists will be included in the subject's source documents. For further details regarding the ASQ-3~~, CBCL/1.5–5, and M-CHAT-R/F,~~ refer to the SPM.

An overview for the collection and review of data for the ASQ-3 is provided in Figure 3.

Figure 3 ~~Ages and Stages Questionnaire-3~~ **ASQ-3, M-CHAT-R/F, and CBCL/1.5–5**: Flow Chart of Data Collection and Review

NOTE: Because of the number of changes to Figure 3 and in order to provide a clear representation of the changes to this figure, the figure in original protocol (2014-MAY-14) and revised figure in Amendment 1 are shown below.

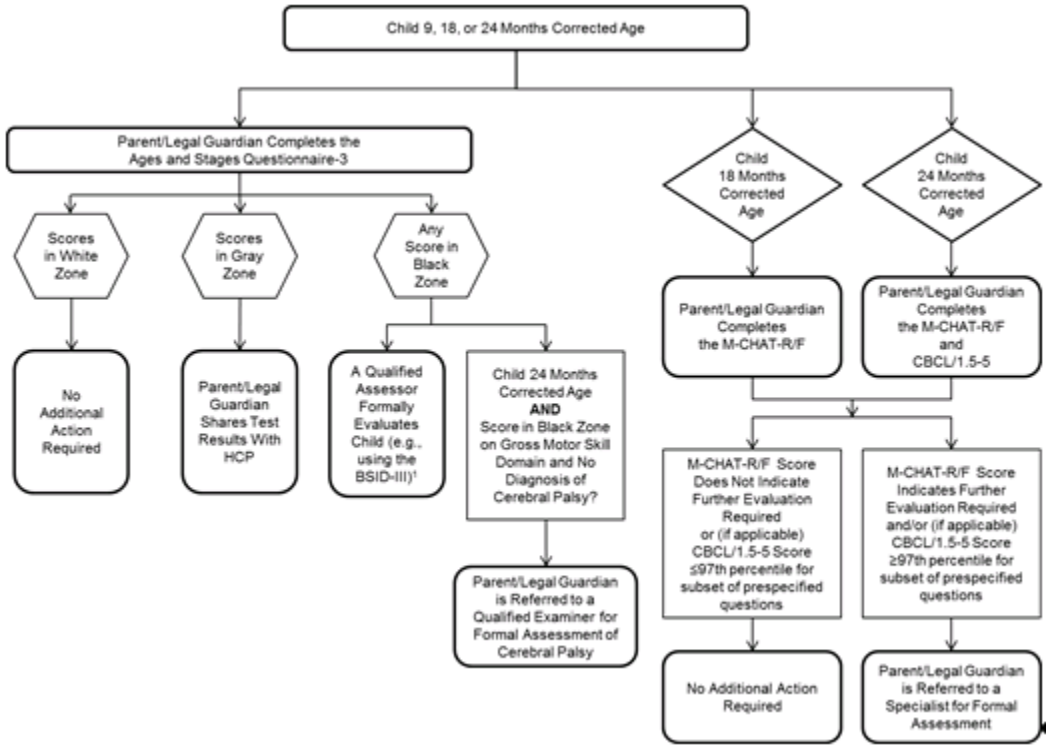
Original Figure:



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; HCP = health care provider; M-CHAT-R/F = Modified Checklist for Autism in Toddlers-Revised with Follow-Up; RCC-PI = research coordinating center-principal investigator.

1. A neurologic examination will also be conducted, if indicated.

New Figure:



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; HCP = health care provider; M-CHAT-R/F = Modified Checklist for Autism in Toddlers-Revised with Follow-Up; RCC-PI = research coordinating center-principal investigator.

1. A neurologic examination will also be conducted, if indicated.

Section 6.2.5.2., Neurodevelopment

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.

- Proportion of infants with a BSID-III score ~~<~~>2 SDs below the mean score for cognitive impairment (<70)
- Proportion of infants with a BSID-III score ~~<~~>2 SDs below the mean score for the gross motor scale (<70)
- Proportion of infants with a BSID-III score ~~<~~>2 SDs below the mean score for the fine motor scale (<70)
- Proportion of infants with a BSID-III score ~~<~~>2 SDs below the mean score for the language scale (<70)
- ~~Proportion of infants referred for an additional behavioral assessment using the CBCL/1.5-5 and M-CHAT-R/F~~
- Proportion of infants with a CBCL/1.5–5 at or-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

Section 6.2.6., Overall Measure of Neurodevelopmental Impairment

- Proportion of infants with at least 1 of the following indicators of neurodevelopmental impairment ~~at the end of the~~:
  - 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 defined as grade 2 or 3 and severe defined as grade 4 or 5 using the Gross Motor Functional Classification System [GMFCS]) **(at 24 months corrected age)**
  - Cognitive impairment: BSID-III Cognitive Scale Score of >2 SDs below mean score (<70) **(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)**

- Proportion of infants and children with at least 1 of the following indicators of neurodevelopmental impairment at the end of the study:
  - **Hearing impaired, uncorrected even with aids**
  - **Blindness in 1 or both eyes, or sees light only**
  - **Cerebral palsy (moderate and severe)**
  - **Diagnosis of ASD, ADD, or ADHD**

Section 6.2.7., Adverse Events

The RCC-PI or RCC site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an SAE. Nonserious AEs will not be tracked.

The outcomes for this study may represent a number of potential adverse drug experiences or events that include but may not be limited to the following:

- Reports of ~~infant~~ **child** hospitalizations (see Section 6.3)
- Reports of chronic health conditions in the ~~infant~~ **child** (see Section 6.2.2)
- Reports of congenital anomalies in the ~~infant~~ **child** (see Section 6.2.3)
- Reports of ~~infant~~ **child** death (see Section 6.2.4)
- Reports of developmental delays in the ~~infant~~ **child** (see Section 6.2.5.2)
- Reports of any other SAEs in the ~~infant~~ **child** ~~for which there is a definite or a reasonable possibility of attribution to retosiban or comparator exposure~~ (see Section 6.2.7.2)

Section 6.2.8., Laboratory and Other Safety Assessment Abnormalities Reported as SAEs

Any ~~nonprotocol-specified~~ abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiograms, radiological scans, vital sign measurements), including those that worsen from Baseline, felt to be clinically significant in the medical and scientific judgment of the RCC-PI are to be recorded as SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the RCC-PI to be more severe than expected for the subject's condition, are not to be reported as SAEs.

Section 6.2.10., Death Events

The proportion of ~~infant~~ deaths that occur~~red~~ after 28 days post EDD and up ~~to 24 months corrected age (for preterm infants) or 24 months~~ **5 years** chronological **age** ~~(for term infants)~~ will be collected.

Section 6.2.11., Time Period and Frequency of Detecting SAEs

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

~~Infant~~ **Child** SAEs will be collected from after 28 days post EDD until ~~24 months corrected age for preterm infants and 24 months~~ **5 years** chronological age ~~for term infants. However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to the end of the study, i.e., month 24.~~ All SAEs will be reported to GSK**/PPD** within 24 hours, as indicated in Section 6.2.12.

Section 6.2.13., Follow-up of SAEs

Any SAEs or AEs of special interest that were ongoing at the end of the Phase III treatment studies and any new SAEs reported during this study will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

Section 6.2.15.2., *Ad Hoc* Maternal Reports

It is possible that during contact with the study staff (RCC staff or RCC-PI), the mother of the ~~infant~~ **child** being followed in this study may report her own AEs/SAEs resultant from retosiban or comparator treatment from Phase III SPTL treatment studies in an ad hoc manner to the RCC study staff or the RCC-PI. The RCC-PI will be responsible for conveying such events to the Phase III SPTL treatment study investigator where the intervention was given to ensure that all safety outcomes are captured.

Section 6.3., Health Outcomes

Resource utilization endpoints include the following:

- 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 the end of the study**.
- 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 the end of the study**.
- Number of surgical procedures (~~by~~ **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 the end of the study**.

- 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**.

Section 6.3.1., Parent/Legal Guardian-Completed Productivity Questionnaire

During the first 24 months of participation in the study, ~~I~~if the infant's parent/legal guardian reports in one of the CHI questionnaires that the child is being treated by a specialist or has had emergency department visits or hospitalizations, they will be asked to complete the productivity questionnaire.

Section 7.1., Data Handling Conventions

For this study, ~~infant~~ **child** data will be entered into GSK/PPD defined eCRFs, transmitted electronically to GSK/PPD, and combined with data provided from other sources e.g., data obtained directly from the parent/legal guardian via an electronic device provided by the sponsor, its designated vendor, or the patient's own devices using a secure and validated data system. The RCC staff will enter data provided on paper into the specifically designed eCRF pages.

Section 7.1.2., Loss to Follow-Up

~~Infants~~ **Children** for whom follow-up information is never obtained will be considered lost to follow-up. These cases will be tallied in the applicable sections of the study reports. All other cases with some follow-up data will be analyzed up to the length of ~~infant~~ **child** follow up.

Section 7.2., Validation Procedures

The ongoing data collection from parents/legal guardians will follow a specific script to elicit information from contacts with the health care system. The ~~infant's~~ **child's** HCP will also be contacted to provide data on the ~~infant's~~ **child's** health and resource utilization when triggered by information from the parent/legal guardian. As indicated in the previous sections, for conditions or events that may meet SAE criteria, medical confirmation and/or medical records will be obtained to provide details of the conditions. All study data will be captured in carefully designed eCRFs specific to the study objectives.

Section 8.1., Hypotheses

The objective of the study is to describe the safety and morbidity and mortality outcomes of ~~infants~~ **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 Section 6.2) will be descriptively summarized.

Section 8.3.4., Interim Analysis

In the event of early stopping of the Phase III SPTL development program due to safety and/or lack of efficacy, ~~infants~~ **children** will continue to be followed until they have ~~reached 24 months corrected age for preterm infants and 24 months~~ **5 years** chronological age ~~for term infants~~.

Section 8.3.5.1.1., Outcomes

The primary objective of the planned analysis will be to use descriptive statistics to describe the safety and morbidity and mortality outcomes of ~~infants~~ **children** exposed to treatment during the Phase III SPTL studies investigating retosiban or comparator for the treatment of SPTL. The endpoints to be descriptively summarized are those described in Section 6.2. Descriptive statistics will be calculated by treatment group and by treatment group and time, where appropriate.

For binary outcomes, all summary tables will include the number and percentage of subjects with the response/event. The associated 95% CI will also be reported. For those endpoints that occur in more than 5 ~~infants~~ **children** or 1% of the ~~infants~~ **children** in any treatment group, odds ratios and associated 95% CIs will be calculated to compare retosiban to placebo, atosiban, and pooled comparator treatment groups. For continuous variables, all summary tables will include: n, mean, median, standard deviation, minimum and maximum. All summary tables will include N for each group (i.e., the total number of subjects randomized to each group within the appropriate population).

To characterize the clinical safety in terms of neurodevelopment in ~~infants~~ **children** exposed to retosiban or comparator, the proportion of ~~infants~~ **children** with at least 1 of the indicators of neurodevelopmental impairment (see Section 6.2.6) at the end of the study will be analyzed using a logistic regression model. The model will use a logit link function to estimate the log odds of percentage of ~~infants~~ **children** with indicators of neurodevelopmental impairment. The model will include terms for treatment group. The number and percentage of subjects in each treatment group, the odds ratios of response rates (retosiban versus placebo, retosiban versus atosiban, and retosiban versus all comparators) and the 95% CIs for the odds ratio of response rates and p values will be presented. The analysis may be repeated for each of the individual indicators of neurodevelopmental impairment.

To further describe the infant safety profile of retosiban, the following subgroups may be explored:

- Gestational age of pregnancy at randomization
- **Established progesterone use (yes or no)**
- **Magnesium sulfate use**
- **Tocolytic use following study drug discontinuation**
- Maternal age
- Region

For each subgroup, ~~infant~~ **child** safety data will be summarized by treatment and subgroup, as previously described. Full details of all planned analyses will be provided in the RAP.

Section 9.2.1., Release of Participant Medical Information

In order to collect data from the participant's HCPs, medical release forms for each clinician who will report data to the study must be completed and signed by the ~~infant's~~ **child's** parent/legal guardian.

Section 9.2.2., Subject Confidentiality

Each participant's identity will be known only to the third-party contractor, RCC-PIs, and relevant HCPs (e.g., pediatrician or specialist). ~~Infant~~ **Child** identification numbers will be assigned and used to identify study participants. The dataset used in the analysis of data will contain coded participant identifiers only.

Section 9.5., Study and RCC Site Closure

Recruitment in participating countries will begin with initiation of the Phase III SPTL treatment studies. Recruitment will continue until the Phase III SPTL treatment studies end recruitment. Follow-up will continue until each child enrolled completes the **5-year** ~~24 month~~ questionnaire at ~~either 24 months corrected age (for preterm infants) or 24 months~~ **5 years** chronological age ~~(for term infants)~~. Study close-out and final reporting activities will be initiated on completion of the follow-up on the last study participant.

Section 9.7., Provision of Study Results to RCC-PIs, Posting of Information on Publicly Available Clinical Trials Registers and Publication

GSK will also provide the RCC-PI with the full summary of the study results. The RCC-PI is encouraged to share the summary results with the parent/legal guardian of the participating ~~infant~~ **child**, as appropriate.

Section 10., References

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

Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Mathews TJ. Births: final data for 2013. Natl Vital Stat Rep. 201~~3~~**5**;6~~2~~**4**(~~9~~**1**):1-~~87~~**65**.

Thornton S, Miller H, Valenzuela G, et al. Treatment of spontaneous preterm labour with retosiban: a phase 2 proof-of-concept study. Br J Clin Pharmacol. 2015 Mar 27. DOI: 10.1111/bcp.12646. [Epub ahead of print].

Protocol Amendment Number 02

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

- Reduction of study duration from 5 years to 24 months due to:
  - Termination of the retosiban development program, such that there will be no further in utero exposure to retosiban, and hence safety data from this ongoing study will not inform the potential risk for future use of retosiban.
  - Low recruitment for interventional studies 200719 (NEWBORN-1) and 200721 (ZINN). Hence, the number of infants exposed to retosiban in utero and included in the current (200722) study is small.
  - The independent data monitoring committee (IDMC) recommendation that the neonatal follow-up be limited to 24 months of age given no safety issues detected in their unblinded review of available 200722 data and also that statistical analysis at a 5-year timepoint would not provide any meaningful results due to the small number of enrolled subjects.
- Reclassification of all resource utilization endpoints as exploratory endpoints due to the reduced sample size
- Correction of an error in the mean BSID-III score for the cognitive impairment, fine motor and gross motor scales to <4 to reflect that these are not composite scores
- Incorporation of other administrative changes

Justification for the Reduction of the ARIOS Study Duration from 5 Years to 24 Months

The objective of the ARIOS long-term follow-up study was to enable the collection of safety data from infants exposed to retosiban in utero for preterm labor to support the Phase 3 data package. The design and duration of 5 years was agreed with the regulators, including the FDA, PMDA and the EMEA. The collection of data in a clinical trial setting would have helped to better inform potential safety concerns prior to approval and treatment of an expanded population in the post-marketing setting. In May 2017, the corresponding treatment trials 200719 (placebo comparison) and 200721 (atosiban comparison) were terminated early due to poor recruitment that made completion of the trials unfeasible in a reasonable timeframe. The placebo-controlled trial enrolled only 23 of the target 900 participants over 17 months, and the atosiban comparator trial enrolled 97 of the target 330 participants over 29 months. Maternal, fetal, and neonatal AEs were no more common with retosiban than placebo or atosiban in this small dataset. GSK also terminated the overall development of retosiban in May 2017, with no further development for this asset either in women in spontaneous pre-term labor or any other indication. Thus, there will be no further in utero exposure in a clinical trial or a post-marketing setting for which there would be a need to inform potential risks.

Due to the early termination of 200719 and 200721, the sample size of ARIOS is small with a total of 98 babies enrolled (6 placebo treated subjects from NB-1, 43 atosiban treated subjects from ZINN and 49 retosiban treated subjects from NEWBORN-1 and ZINN). This represents just 8% of the planned 1230 infants that were to be enrolled in the study. The intent of the design of ARIOS was to compare data from the retosiban exposed group in each of the treatment trials to the placebo exposed group. In order to accomplish this, data from both 200719 and 200721 were to be pooled from all the babies exposed to retosiban and compared against placebo-exposed babies. As there were only 6 babies exposed to placebo with the drop-out rate expected to increase as the study progresses, the sample size will not be sufficient to permit a meaningful comparison of long-term safety between active treatment and placebo subjects if the follow-up study was continued for 5 years of follow-up.

On 28 August 2018, the retosiban IDMC, composed of 1 pediatrician, 2 neonatologists, 2 maternal-fetal medicine specialists and a statistician, confirmed that there were no safety concerns identified following review of ZINN and NEWBORN-1 clinical study reports as well as ARIOS adverse events (including congenital anomalies), neurodevelopment screening assessments (ASQ-3, CBCL/1.5-5, and MCHAT-R/F), and neurodevelopment referrals, from an ARIOS data cut on 15 June 2018, with 34 out of a total of 98 babies having already completed 24 months of safety follow-up. The IDMC also recommended that the neonatal follow-up be limited to 24 months of age given that the small number of enrolled subjects, in particular placebo subjects for comparison, would not yield meaningful results. Twenty-four months, in the IDMC collective opinion, would allow for detection of major neonatal adverse outcomes and safety signals and as such would be sufficient, especially considering that there will be no future development of retosiban.

Furthermore, 24-month outcomes are considered by the experts in the field to be appropriate for safety assessment (Marlow, 2014). Dr. Neil Marlow, who is an IDMC member, in collaboration with regulatory agencies, has developed a manuscript (in press) that recommends that 24-month follow-up is appropriate for safety follow-up in this population.

Reduction of the study duration from 5 years to 24 months will not impact the care of the infant as they will still follow neonatal and pediatric developmental screening standard of care as prescribed by their pediatrician or health care provider following completion of the study. Therefore, there is no safety risk to the neonate by reducing the study follow-up period from 5 years to 24 months.

Administrative changes

Other administrative changes were incorporated into this amendment. The rationale for these changes is to ensure a clear and complete protocol for use at the RCC sites.

Specific Changes in the Text

Title Page:

Authors (GSK): PPD

Authors (PPD): PPD

SPONSOR SIGNATORY

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

Rajnish Saini, MD
Clinical Director,
Future Pipeline Discovery
Global Health R&D

SPONSOR INFORMATION PAGE

Sponsor Medical Monitors and Serious Adverse Events (SAEs) Contact Information

Issue	North America Contract	Latin America Contact	Europe/Asia Contact
Safety Questions	PPD, ~~MD~~ ~~Medical Director, Medical Affairs and Pharmacovigilance~~ ~~PPD~~ ~~Wilmington, NC, USA~~ PPD, **MD, MPH** **Associate Medical Director, Medical Affairs and Pharmacovigilance** **PPD** **Denver, CO, USA**	PPD, MD Medical Director, Medical Affairs and Pharmacovigilance PPD Buenos Aires, Brazil	Europe: PPD, MD Associate Medical Director, Medical Affairs and Pharmacovigilance PPD Sofia, Bulgaria Asia: PPD, MD Associate Medical Director, Medical Affairs and Pharmacovigilance PPD Kuala Lumpur, Malaysia
SAE Reporting	24-Hour Safety Hotline: PPD Safety Fax: PPD	24-Hour Safety Hotline: PPD Safety Fax: PPD	24-Hour Safety Hotline: PPD Safety Fax: PPD

PROTOCOL SUMMARY, Rationale

The goal of this study (ARIOS), therefore, is to assess the safety and outcomes of infants and children who were exposed to retosiban (GSK221149) or comparator in utero in the ~~planned~~ Phase III SPTL treatment studies and provide assurance that treatment is not associated with significant adverse outcomes in early childhood.

In May 2017, the corresponding treatment trials 200719 (NEWBORN-1, placebo comparison) and 200721 (ZINN, atosiban comparison) were terminated early due to poor recruitment and the length of time needed to complete the studies. The placebo-controlled trial enrolled only 23 of the target 900 participants over 17 months, and the atosiban comparator trial enrolled 97 of the target 330 participants over 29 months. Maternal, fetal, and neonatal adverse events were no more common with retosiban than placebo or atosiban. The development program was subsequently terminated with no further in utero exposure of retosiban planned.

PROTOCOL SUMMARY, Objectives

Primary

- 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
- To characterize the clinical safety in terms of neurodevelopment in infants and children exposed to retosiban or comparator in utero

Exploratory

- To characterize parental productivity loss related to a sick child and infant resource utilization in terms of hospital admissions, length of stay, emergency room/urgent care (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

PROTOCOL SUMMARY, Study Design

Infants and children will be followed at prespecified intervals until they have reached ~~5 years~~ **24 months** chronological age.

The child's parent/legal guardian will be asked to complete a Child Health Inventory (CHI) at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological ~~age and a modified CHI at 3, 4, and 5 years of the child's chronological age.~~ The CHI questionnaire completed up to the 24-month time point will screen for infant mortality and morbidity and will capture data on resource utilization. ~~At the 3-, 4-, and 5-year time points, the CHI will screen for child mortality and morbidity, including any indicators of neurodevelopmental impairment.~~

During the ~~first~~ 24 months of participation in the study, if the parent/legal guardian indicates that the infant has been treated by specialists or has had ER/UC visits or hospitalizations, he/she will be asked to complete a productivity questionnaire to evaluate loss of parental productivity.

If at any of these time points a child has an M-CHAT-R/F score that indicates further evaluation is required and/or a CBCL/1.5–5 score ~~at or~~ above the 97th percentile for a subset of prespecified questions, the child will be referred to a specialist for a formal assessment.

PROTOCOL SUMMARY, Study Endpoints/Assessments

Study **primary** endpoints include the following and are further defined in Section 6.2.2:

Morbidity and mortality endpoints:

- 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
  - Neurological conditions
  - Sensory conditions
  - Gastrointestinal conditions
  - Cardiovascular conditions
  - Renal conditions
  - Growth parameters ~~(only up to 24 months chronological age)~~
- Proportion of infants and children with newly diagnosed (after 28 days post EDD) congenital anomalies
- Proportion of infant and child deaths after 28 days post EDD and until ~~the end of the study~~ **24 months chronological age**

Neurodevelopment endpoints:

- Proportion of infants with a BSID-III score >2 SDs below the mean score for the cognitive impairment (<~~70~~ **4**)
- Proportion of infants with BSID-III score >2 SDs below the mean score for the gross motor scale (<~~70~~ **4**)
- Proportion of infants with BSID-III score >2 SDs below the mean score for the fine motor scale (<~~70~~ **4**)

- Proportion of infants with a BSID-III score >2 SDs below the mean score for the language scale (<~~70~~ **70**)
- Proportion of infants with a CBCL/1.5–5 score ~~at or~~ above the 97th percentile for a subset of prespecified questions that relate to attention and hyperactivity problems

- Cognitive impairment: BSID-III Cognitive Scale Score of >2 SDs below mean score (<~~70~~ **4**) (at 24 months corrected age)
- Motor impairment: BSID-III Motor Composite Scale Score of >2 SDs below mean score (<~~70~~ **70**) (at 24 months corrected age)

- ~~Proportion of infants and children with at least 1 of the following indicators of neurodevelopmental impairment at the end of the study:~~
  - ~~Hearing impaired, uncorrected even with aids~~
  - ~~Blindness in 1 or both eyes or sees light only~~
  - ~~Cerebral palsy (moderate and severe)~~
  - Diagnosis of ASD, attention deficit disorder (ADD), or attention deficit hyperactivity disorder (ADHD)

~~Resource~~ **Exploratory resource** utilization endpoints **include**:

- 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., **neonatal intensive care unit** [NICU**],** Pediatric, **pediatric intensive care unit [**PICU**]**, Nursery level 3, **intensive care unit [**ICU~~)~~**])**, and length of hospital stay per unit after 28 days post EDD and until ~~the end of the study~~ **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 ~~the end of the study~~ **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 ~~the end of the study~~ **24 months chronological age**.

Section 1.1, Background

Retosiban ~~is~~ **was** being developed for the treatment of spontaneous preterm labor (SPTL) in women with intact membranes.

Phase III SPTL treatment studies ~~will be~~ **were** conducted to demonstrate the ability of retosiban to prolong pregnancy and improve neonatal health, as well as to describe the maternal, fetal, and neonatal safety profiles. **The treatment studies were subsequently terminated due to limited recruitment and the development program was subsequently terminated with no further in-utero exposure planned.**

Section 1.1.1, Previous Human Experience

Study OTA105256 was the first Phase II clinical study of retosiban in preterm labor (n=93) [Thornton, 2015; GlaxoSmithKline Document Number CM2006/00201/~~03~~**06**].

~~The emerging safety profile for retosiban appears favorable. Results from protocol-specified maternal-fetal and neonatal safety assessments were absent of any concerns and were similar between the retosiban and placebo groups. Furthermore, no clinically significant disparities in AEs were noted between groups [Thornton, 2015]. All reported AEs, whether maternal, fetal, or neonatal, were generally consistent with those reported in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number CM2006/00201/03], IB Supplement 1 [GlaxoSmithKline Document Number 2015N228508_00], or in the study population.~~

The Phase 3 program included 2 global blinded, randomized, controlled trials (200721 [ZINN] and 200719 [NEWBORN-1]) and a single infant follow-up trial (200722 [ARIOS]). Eligible subjects were aged 12 to 45 years with an uncomplicated singleton pregnancy and intact membranes in spontaneous preterm labor at $24^{0/7}$ to $33^{6/7}$ weeks' gestation. ZINN (N=330) aimed to show superiority of retosiban (IV) over atosiban on time to delivery (first subject first visit [FSFV] was March 2015). NEWBORN-1 (N=900) was designed to demonstrate neonatal benefit (based on a composite endpoint) as well as time to delivery or time to treatment failure over placebo (FSFV February 2016). The intervention trials were terminated early on 11 May 2017 because of slow recruitment and the retosiban project was discontinued permanently. Last subject last visit (LSLV) was 24 July 2017 for NEWBORN-1 and 25 August 2017 for ZINN. Meaningful analyses of these well-controlled trials could not be performed due to small numbers of completing participants. Mean time to delivery or treatment failure in the placebo-controlled trial was 18.9 days with retosiban (n=10) versus 11.1 days with placebo (n=13). Two neonates in the retosiban and 4 in the placebo group had ≥1 component of the neonatal composite endpoint. The adjusted mean time to delivery in the atosiban comparator trial was 32.51 days with retosiban (n=50) compared with 33.71 days with atosiban (n=47; $P>0.05$). Maternal, fetal, and neonatal AEs were no more common with retosiban than placebo or atosiban.

In NEWBORN-1, 1 participant in the retosiban group provided cord blood and breast milk samples; retosiban was found in both (cord blood, 1.9 µg/L; breast milk, 3.6 µg/L). In ZINN, 12 women in the retosiban group provided cord blood samples, none of which had detectable levels of retosiban. One participant also provided a breast milk/colostrum sample. The retosiban concentration was 0.3 µg/L.

Section 1.2, Rationale

The goal of this study (ARIOS), therefore, is to assess the safety and outcomes of infants and children who were exposed to retosiban or comparator in utero in the ~~planned~~ Phase III SPTL treatment studies and provide assurance that treatment is not associated with significant adverse outcomes in early childhood.

Section 1.3, Benefit:Risk Assessment

Summaries of findings from both clinical and nonclinical studies conducted with GSK221149 can be found in the IB and the Phase III SPTL treatment **clinical** study ~~protocols~~ **reports**.

Section 1.3.1, Risk Assessment

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

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
	For both NEWBORN-1 and ZINN, cord blood samples were requested from subjects who delivered at the investigative center within 12 hours after discontinuation of study drug. Samples were only analyzed for subjects randomized to retosiban. A total of 4 cord samples were collected within NEWBORN -1 (3 placebo: 1 retosiban) and 27 within ZINN (12 retosiban: 15 atosiban). Within both studies, only 1 cord blood sample tested positive for retosiban at a concentration of 1.9 µg/L. The 1.9 µg/L is approximately 0.006x to 0.01x the cord blood concentrations that were observed in the pregnant monkey toxicity studies (cord blood concentrations = 159 to 313 µg/L). There were no adverse effects observed in the offspring in monkey studies, where growth and development included a full assessment of reflexive behaviors, infant ECG and blood chemistry were analyzed. Furthermore, a rat post-natal study starting in juvenile rats that were 1 day old did not show any adverse effects on growth and development, including neurobehavior and reproductive assessments at exposure levels that were approximately 800-fold of what was observed in the cord blood (gender averaged Cmax = 1535 µg/L). Day 1 old rats were used in this study as they were developmentally similar to late third-term human fetuses. The overall animal data indicate that potential risk for a fetus exposed gestationally to retosiban is negligible.	

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
Neonatal exposure via breast milk	~~While there are no clinical data on the degree of retosiban transfer into breast milk, the available data based on physiochemical properties suggest retosiban will be excreted into breast milk if dosed close to or during the time of milk production. Given the rapid clearance of retosiban, the risk for neonatal drug exposure via breast milk appears low but could occur in the situation where the infant is fed breast milk/colostrum produced within 12 hours of treatment. Since lactogenesis is typically delayed 30 to 48 hours postpartum in mothers going to term (and is further delayed in mothers who deliver preterm), it seems unlikely that any drug would be in the plasma postpartum to transfer into the milk.~~	Breast milk/colostrum samples ~~will be~~ **were** collected for measurement of retosiban when delivery ~~occurs~~ **occurred** and lactation ~~has~~ **had** started within 12 hours of receiving study treatment infusion as part of the Phase III SPTL treatment studies. Infants exposed to retosiban via breast milk will be followed for up to ~~5 years~~ **24 months** in this study to assess safety and neurodevelopmental outcomes.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Retosiban [e.g., GSK221149]		
	Positive breast milk samples were detected within 1 maternal subject in NEWBORN-1 and 1 subject in ZINN, with the highest concentration being 0.36 µg/L. Assuming a standardized milk consumption of 0.150 L/kg/day (the mean milk intake of a fully breast-fed 2-month old infant [Begg, 1999; Bennett, 1988; Hagg, 2000; Kristensen, 1999]), the worst-case dose of retosiban that a breast-fed child would be exposed to is 0.54 µg/kg/day (3.6 µg/L x 0.15 L/kg/day). This is approximately 0.5% of the human dose. This is the worst-case scenario because the mother is not being administered retosiban post-partum during the lactation period, and retosiban is cleared rapidly, which would rapidly diminish the amount retosiban present circulation and in the milk. Furthermore, based on body surface area, this potential infant dose is greater than 8000-fold, the dose where no adverse effects were seen in growth and development in the rat post-natal development study (rat post-natal development study NOAEL = 30 mg/kg/day; human equivalent dose = 4800 µg/kg/day). The potential lactational dose of retosiban that would therefore pose any significant risk to a newborn is negligible.	

ECG = electrocardiogram; NOAEL = no-observed-adverse-effect-level; SPTL = spontaneous preterm labor.

Section 1.3.2, Benefit Assessment

Given the inverse relationship between the risks for prematurity complications and gestational age at birth, the development of a treatment that significantly prolongs pregnancy in women with SPTL would be invaluable if associated with improved perinatal outcomes. Results from the Phase II study OTA105256 offer hope that retosiban may prolong pregnancy to such a degree that perinatal outcomes could be favorably affected [Thornton, 2015]. ~~There are currently no safety findings that would preclude~~

~~further development of retosiban for an indication for the treatment of SPTL in conjunction with standard of care treatments in women with an uncomplicated, singleton pregnancy~~ **However, the results from the Phase III interventional studies did not provide compelling evidence that retosiban could prolong time to delivery of retosiban relative to placebo or atosiban, but because of the low enrollment numbers and inadequate statistical power, results should be interpreted with caution**.

The benefit to infants and children participating in this study is the focus on following morbidity and neurodevelopment for up to ~~5 years~~ **24 months** following exposure to retosiban or comparator medication.

Section 1.3.3, Overall Benefit:Risk Conclusion

For detailed information on the identified risks and benefit:risk assessment of retosiban, refer to the **Investigator's Brochure (**IB**)** ~~and IB Supplement 1~~ [GlaxoSmithKline Document Number CM2006/00201/~~03~~**06**~~; GlaxoSmithKline Document Number 2015N228508_00~~]. ~~Although, experience in pregnant women is limited, no clinical or preclinical safety issues have been identified that preclude further development.~~

Table 1, Summary of Study Objectives and Corresponding Endpoints

Objective	Endpoints
Primary	•

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 ~~(only up to 24 months chronological age)~~
	  ○ 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 the ~~end of the study~~ **24 months chronological age**

Objective	Endpoints

~~To characterize the clinical safety in terms of neurodevelopment in infants and children exposed to retosiban or comparator in utero~~	• 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 (<~~70~~ **4**)
	  • Proportion of infants with BSID-III score >2 SDs below the mean score for the gross motor scale (<~~70~~ **4**)
	  • Proportion of infants with BSID-III score >2 SDs below the mean score for the fine motor scale (<~~70~~ **4**)
	  • Proportion of infants with a BSID-III score >2 SDs below the mean score for the language scale (<~~70~~ **70**)
	  • Proportion of infants with a CBCL/1.5-5 score at or 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)
	  • Cognitive impairment: BSID-III Cognitive Scale Score of >2 SDs below mean score (<~~70~~ **4**) (at 24 months corrected age)
	  • Motor impairment: BSID-III Motor Composite Scale Score of >2 SDs below mean score (<~~70~~ **70**) (at 24 months corrected age)
	• ~~Proportion of infants and children with at least 1 of the following indicators of neurodevelopmental impairment at the end of the study:~~
	  • ~~Hearing impaired, uncorrected even with aids~~
	  • ~~Blindness in 1 or both eyes, or sees light only~~
	  • ~~Cerebral palsy (moderate and severe)~~
	  • Diagnosis of ASD, ADD, or ADHD

Objective	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 ~~the end of the study~~ **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 ~~the end of the study~~ **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 ~~the end of the study~~ **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

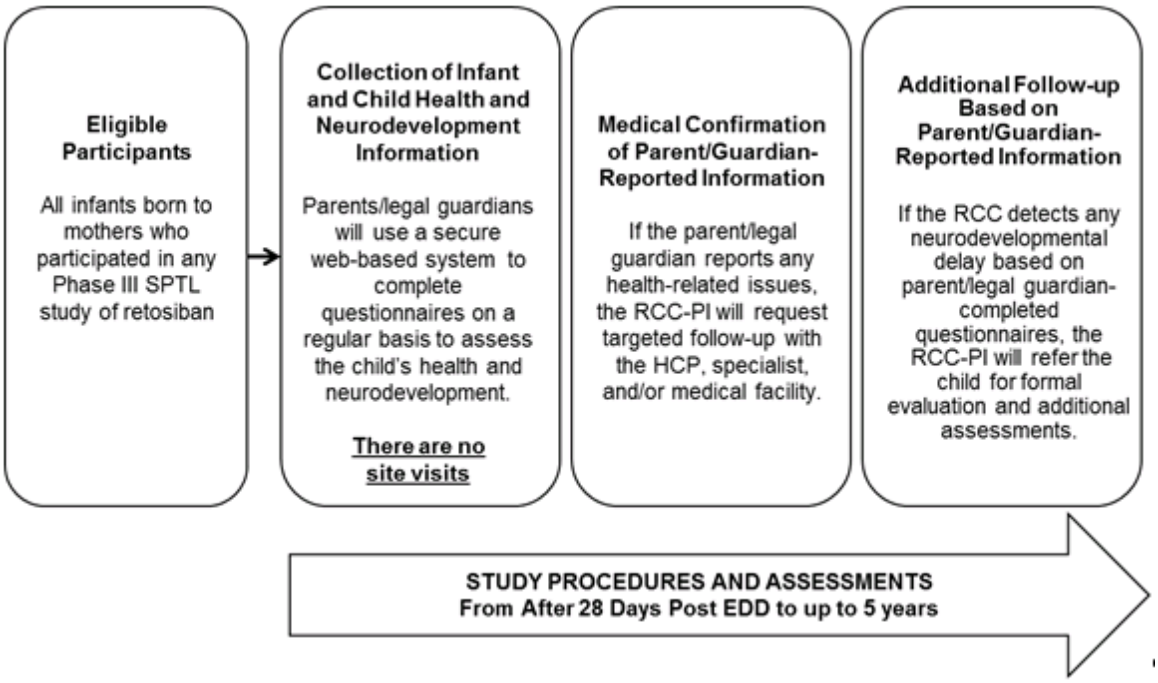
ADD = attention deficit disorder; ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; ASQ-3 = Ages and Stages Questionnaire-3; BSID-III = Bayley Scales of Infant Development, third edition; CBCL/1.5-5 = Child Behavior Checklist for Ages 1.5 to 5; EDD = estimated date of delivery; 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.

Section 3.1, Study Design

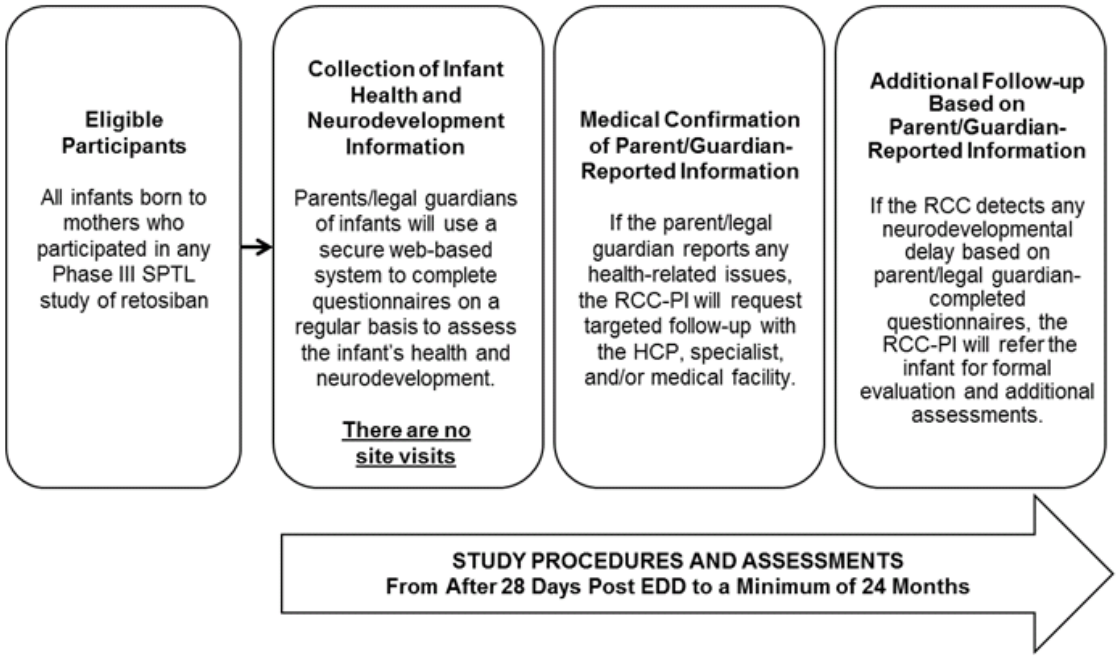
Infants and children will be followed at prespecified intervals until they reach ~~5 years~~ **24 months** chronological age (see Table 2).

Figure 1, Study Design

Original Figure:



Updated Figure:



The child's parent/legal guardian will be asked to complete the CHI at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age ~~and a modified CHI at 3, 4, and 5 years of the child's chronological age~~. The CHI questionnaire completed up to the 24-month time point will screen for infant mortality and morbidity and will capture data

on resource utilization. ~~At the 3-, 4-, and 5-year time points, the CHI will screen for child mortality and morbidity, including any indicators of neurodevelopmental impairment.~~

If protocol-specific evaluations are in progress at the end of the child's protocol-defined participation in this study (~~5 years~~ **24 months** chronological age) and results have not yet been received or reported, the time period may be extended to collect those reports.

During the ~~first~~ 24 months of participation in the study, if the parent/legal guardian indicates that the infant has been treated by specialists or has had ER/UC visits or hospitalizations, he/she will be asked to complete a productivity questionnaire to evaluate loss of parental productivity.

The M-CHAT-R/F will be completed for all infants at 18 and 24 months (corrected age) and the CBCL/1.5–5 will be completed for all infants at 24 months (corrected age) to assess the risk for other behavioral problems or autism spectrum disorder (ASD). If at any of these time points a child has an M-CHAT-R/F score that indicates further evaluation is required and/or a CBCL/1.5–5 score ~~at or~~ above the 97th percentile for a subset of prespecified questions, the child will be referred to a specialist for a formal assessment.

Protocol Amendment 2 has updated the total study duration to 24 months. Babies or infants that have passed the 24-month assessments after the amendment implementation are not required to continue further within the study, nor do they need to complete any subsequent study related assessments. Following completion of the study, the neonates will continue their normal pediatric standard of care with their primary care pediatrician or health care provider.

The 24-month data will form the final study endpoint assessment timing; however, if data has been collected from a baby/infant after they have passed the 24-month endpoint, then this data will be included as a data listing within the clinical report.

Section 4.2, Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB ~~and IB Supplement 1~~ [GlaxoSmithKline Document Number CM2006/00201/~~03~~**06**~~; GlaxoSmithKline Document Number 2015N228508_00~~].

Section 6, Study Assessments and Procedures

The infants and children will be followed beginning from after 28 days post EDD and until ~~5 years~~ **24 months** chronological age.

The timing of the first questionnaire is scheduled to begin at 2 months chronological age and end at ~~5 years~~ **24 months** chronological age.

The EPDS should ideally be completed at 6 weeks (~~±~~ **-**2 weeks**/+6 weeks**) post-delivery but may be completed as early as ~~1~~ **4** week**s** post-delivery or as late as 12 weeks post-delivery.

Table 2, Time and Events Table

Event	28 Days Post EDD	Months								~~Years~~[1]		
		2	6	9	12	15	18	21	24	~~3~~	~~4~~	~~5~~
Written informed consent[2]	◄	———	———	———	———							
Baseline characteristics and demographic data	X[3]											
RCC confirms and updates contact information from the parent/legal guardian	X											
Parent/legal guardian completes CHI[4]		X	X	X	X	X	X	X	X	~~X~~[4]	~~X~~[4]	~~X~~[4]
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[5]		———	———	———	———	———	———	———	——— ►			
Parent/legal guardian completes ASQ-3[6]				X[6]			X[6]		X[6]			
RCC-PI reviews ASQ-3 results and refers for developmental evaluation based on results[7]				———	———	———	———	———	——— ►			
Parent/legal guardian completes M-CHAT-R/F[8]							X		X			
Parent/legal guardian completes CBCL/1.5–5[8]									X			
RCC-PI refers child to specialist for cerebral palsy assessment (if required)[9]									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. Assessments performed at years 3, 4, and 5 are based on the child's chronological age.~~

1. ~~2.~~ 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. ~~3.~~ Captured in Phase III SPTL treatment studies and combined with child follow-up data for analyses.

3. ~~4.~~ 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. ~~A modified CHI will be completed at 3, 4, and 5 years of the child's chronological age.~~ At each time point, the completion window of the CHI is +6 weeks.

4. ~~5.~~ 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. ~~6.~~ 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. ~~7.~~ If the parent/legal guardian receives a referral, then a qualified specialist will complete required assessments.

7. ~~8.~~ 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. ~~9.~~ 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.

Section 6.2.1

The morbidity endpoints will be assessed at 2, 6, 9, 12, 15, 18, 21, and 24 months ~~and 3, 4, and 5 years~~ of the child's chronological age.

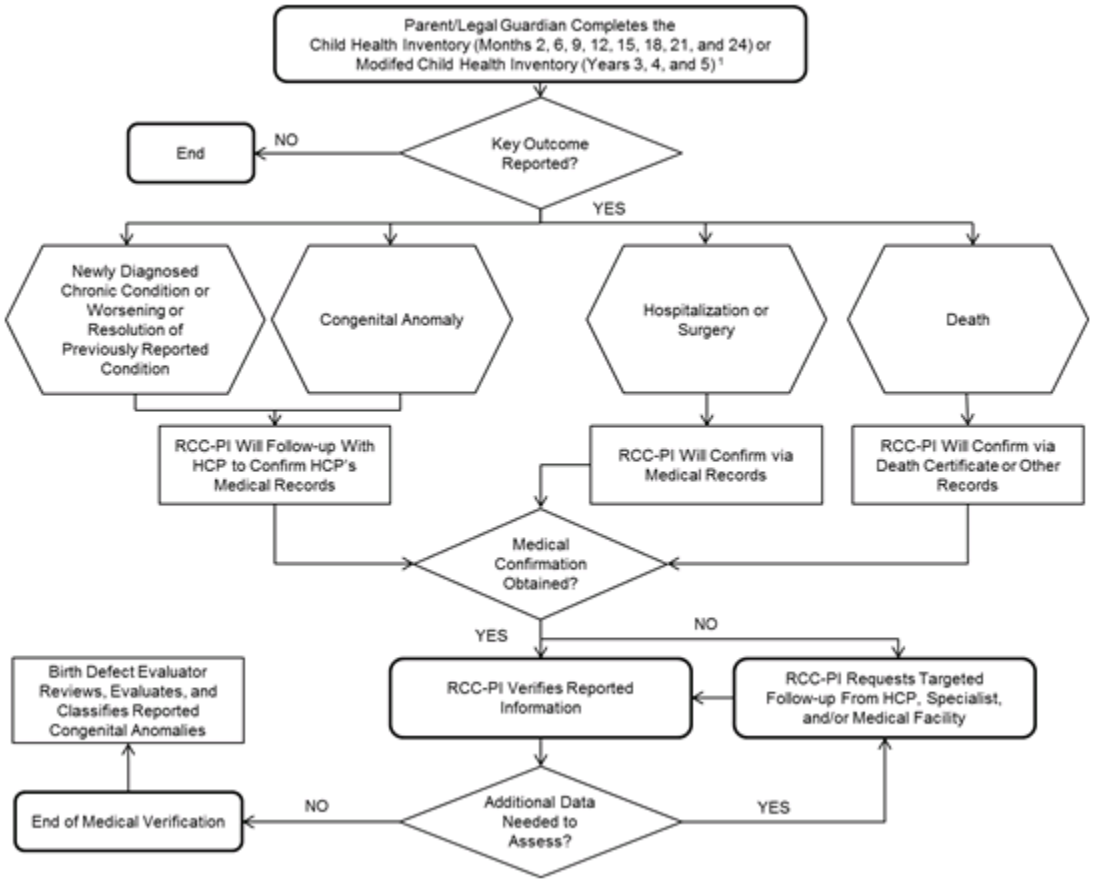
Section 6.2.1.1, Parent/Legal Guardian-Completed Child Health Inventory

The child's parent/legal guardian will be asked to complete the CHI at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age ~~and a modified CHI at 3, 4, and 5 years of the child's chronological age~~. At each time point, the completion window is +6 weeks; however, CHI questionnaires completed outside the completion window will not be considered a protocol deviation.

The CHI administered at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age will screen for infant mortality and morbidity and capture data on resource utilization. ~~At 3, 4, and 5 years of the child's chronological age, the CHI will screen for child mortality and morbidity, including any indicators of neurodevelopmental impairment.~~

Figure 2, Child Health Inventory: Flow Chart of Data Collection and Review

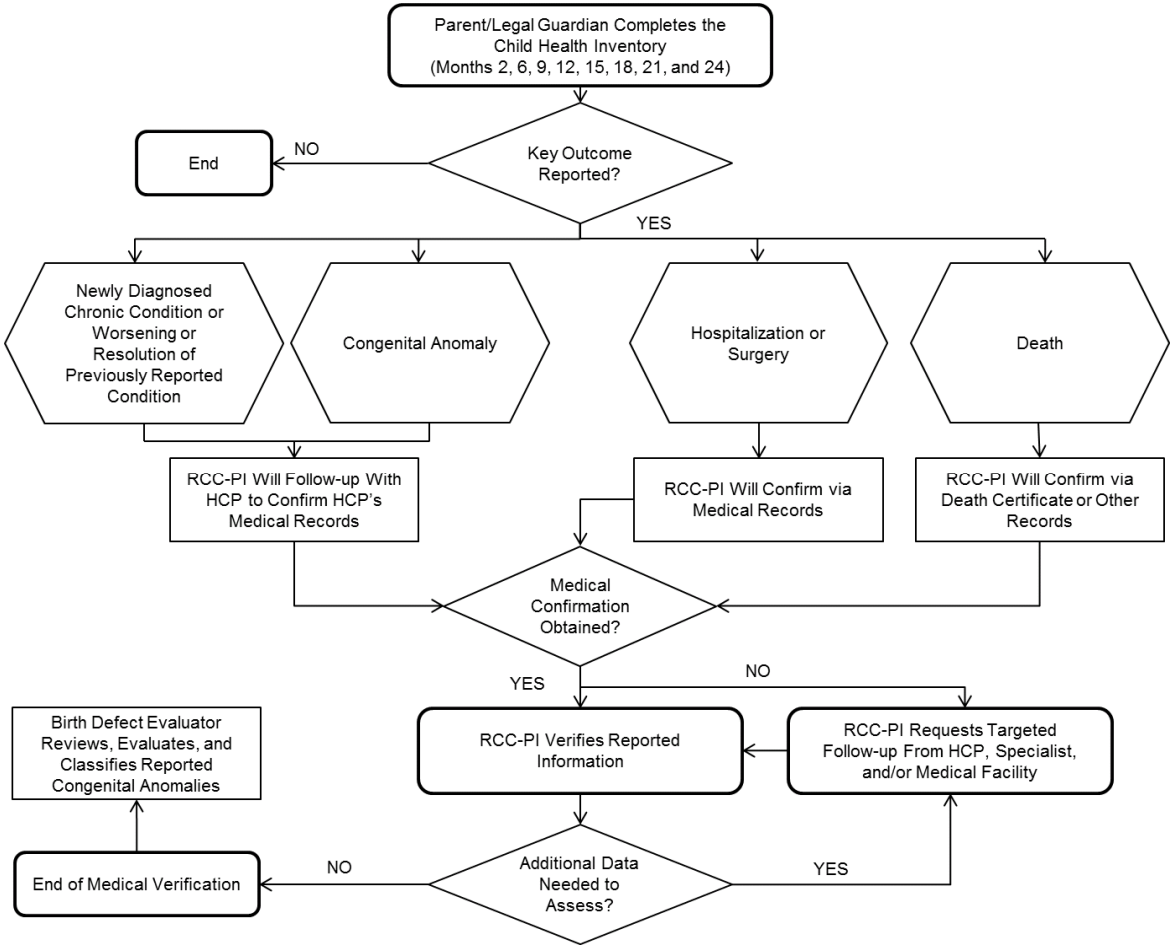
Original Figure:



CHI = Child Health Inventory; HCP = health care provider; RCC-PI = research coordinating center-principal investigator.

1. The CHI completed at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age will screen for infant mortality and morbidity and capture data on resource utilization. At 3, 4, and 5 years of the child's chronological age, the CHI will screen for child mortality and morbidity, including any indicators of neurodevelopmental impairment.

Updated Figure:



CHI = Child Health Inventory; HCP = health care provider; RCC-PI = research coordinating center-principal investigator.

1. The CHI completed at 2, 6, 9, 12, 15, 18, 21, and 24 months of the child's chronological age will screen for infant mortality and morbidity and capture data on resource utilization. ~~At 3, 4, and 5 years of the child's chronological age, the CHI will screen for child mortality and morbidity, including any indicators of neurodevelopmental impairment.~~

Section 6.2.2.7, Growth Parameters

Growth parameters will ~~be assessed only up to 24 months chronological age and will~~ include the following:

Section 6.2.4, Infant and Child Deaths

This study will assess the proportion of infant and child deaths that occur after 28 days post EDD and up to ~~5 years~~ **24 months** chronological age.

Section 6.2.5, Parent/Legal Guardian-Completed ASQ-3, M CHAT R/F, and CBCL/1.5–5 and Possible Referral to a Specialist

If at any of these time points a child has an M-CHAT-R/F score that indicates further evaluation is required and/or a CBCL/1.5–5 score ~~at or~~ above the 97th percentile for a subset of prespecified questions, the child will be referred to a specialist for a formal assessment.

In this study, infants with test scores ~~at or~~ above the 97th percentile for a subset of prespecified questions that relate to attention or hyperactivity problems syndrome or the American Psychiatric Association's Diagnostic and Statistical Manual (DSM)-oriented attention-deficit/hyperactivity disorder scale will be considered to have a behavior problem, which will trigger a referral to a developmental specialist for a formal assessment.

The completion window for the CBCL/1/5-5 and M-CHAT-R/F is +6 week**s** at 18 months (M-CHAT-R/F **only**) and +12 weeks at 24 months; however, questionnaires completed outside the completion window will not be considered a protocol deviation.

Section 6.2.5.2, Neurodevelopment

- Proportion of infants with a BSID-III score >2 SDs below the mean score for cognitive impairment (<~~70~~ **4**)
- Proportion of infants with a BSID-III score >2 SDs below the mean score for the gross motor scale (<~~70~~ **4**)
- Proportion of infants with a BSID-III score >2 SDs below the mean score for the fine motor scale (<~~70~~ **4**)
- Proportion of infants with a BSID-III score >2 SDs below the mean score for the language scale (<~~70~~ **70**)
- Proportion of infants with a CBCL/1.5–5 ~~at or~~ above the 97th percentile for a subset of prespecified questions that relate to attention and hyperactivity problems

Section 6.2.6, Overall Measure of Neurodevelopmental Impairment

- Cognitive impairment: BSID-III Cognitive Scale Score of >2 SDs below mean score (<~~70~~ **4**) (at 24 months corrected age)

- Motor impairment: BSID-III Motor Composite Scale Score of >2 SDs below mean score (<~~70~~ **70**) (at 24 months corrected age)

- ~~Proportion of infants and children with at least 1 of the following indicators of neurodevelopmental impairment at the end of the study:~~
  - ~~Hearing impaired, uncorrected even with aids~~
  - ~~Blindness in 1 or both eyes, or sees light only~~
  - ~~Cerebral palsy (moderate and severe)~~
  - Diagnosis of ASD, ADD, or ADHD

Section 6.2.10, Death Events

The proportion of deaths that occur after 28 days post EDD and up to ~~5 years~~ **24 months** chronological age will be collected.

Section 6.2.11, Time Period and Frequency of Detecting SAEs

Child SAEs will be collected from after 28 days post EDD until ~~5 years~~ **24 months** chronological age. All SAEs will be reported to GSK/PPD within 24 hours, as indicated in Section 6.2.12.

Section 6.2.14, Prompt Reporting of SAEs and Other Events to GSK/PPD

The contact information for reporting SAEs is as follows:

Issue	North America Contract	Latin America Contact	Europe/Asia Contact
Serious Adverse Event Reporting	24-Hour Safety Hotline: PPD Safety Fax: PPD	24-Hour Safety Hotline: PPD Safety Fax: PPD	24-Hour Safety Hotline: PPD Safety Fax: PPD

Section 6.3, Health Outcomes

Resource utilization **exploratory** endpoints include the following:

- 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 the end of the study~~ **up to 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 the end of the study~~ **up to 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 the end of the study~~ **up to 24 months chronological age**.

Section 6.3.1, Parent/Legal Guardian-Completed Productivity Questionnaire

During the ~~first~~ 24 months of participation in the study, if the infant's parent/legal guardian reports in one of the CHI questionnaires that the child is being treated by a specialist or has had emergency department visits or hospitalizations, they will be asked to complete the productivity questionnaire.

Section 8.1, Hypotheses

~~If deemed appropriate, point estimates and associated 95% confidence intervals (CIs) may be calculated for the comparison of retosiban to placebo and retosiban to atosiban for some safety endpoints.~~ No type I error adjustments are planned.

Section 8.2.1, Sample Size Assumptions

The sample size for this study will depend on the total number of subjects enrolled in the Phase III SPTL treatment studies. ~~At~~ **In May 2017**, the ~~time of protocol publishing~~, 2 Phase III SPTL treatment studies ~~are planned that will enroll at total of approximately 1100 mothers. However,~~ **were terminated early due to** the ~~number~~ **feasibility** of ~~studies and/or size of~~ **recruiting** the studies ~~may change depending on~~ **in a timely manner, meaning that** the ~~outcome of the first planned Phase III SPTL treatment study, such that the total number of mothers enrolled could be~~ **size of these studies was lower** ~~or higher~~ than ~~currently planned.~~ **originally planned. This has resulted in a greatly reduced sample size for this study.**

Section 8.3.1, Analysis Populations

The primary population for safety assessment will be all infants **whose mothers have been randomized and received retosiban or comparator in any of the Phase III treatment trials. Of these mothers, the infant safety population includes the mother/infant pairs who** enrolled into the study ~~with at least 1 observation~~**, the mother/infant pairs who decline to consent to the study, and the mother/infant pairs whose fetus/neonates/infants died prior to the enrollment of the study**. Subjects will be analyzed according to their actual treatment in case this differs from their randomized treatment. ~~All analyses will be based on the primary population dataset.~~

Section 8.3.4, Interim Analysis

In the event of early stopping of the Phase III SPTL development program due to safety and/or lack of efficacy, children will continue to be followed until they have reached ~~5 years~~ **24 months** chronological age.

For any subject for which the CHI questionnaire at 3, 4, and 5 years of the child's chronological age was completed prior to Amendment 2, data will be reported.

Section 8.3.5.1.1, Outcomes

For binary outcomes, all summary tables will include the number and percentage of subjects with the response/event. ~~The associated 95% CI will also be reported. For those endpoints that occur in more than 5 children or 1% of the children in any treatment group, odds ratios and associated 95% CIs will be calculated to compare retosiban to placebo, atosiban, and pooled comparator treatment groups.~~ For continuous variables, all summary tables will include: n, mean, median, standard deviation, minimum and maximum. All summary tables will include N for each group (i.e., the total number of subjects randomized to each group within the appropriate population).

~~To characterize the clinical safety in terms of neurodevelopment in children exposed to retosiban or comparator, the proportion of children with at least 1 of the indicators of neurodevelopmental impairment (see Section 6.2.6) at the end of the study will be analyzed using a logistic regression model. The model will use a logit link function to estimate the log odds of percentage of children with indicators of neurodevelopmental impairment. The model will include terms for treatment group. The number and percentage of subjects in each treatment group, the odds ratios of response rates (retosiban versus placebo, retosiban versus atosiban, and retosiban versus all comparators) and the 95% CIs for the odds ratio of response rates and p values will be presented. The analysis may be repeated for each of the individual indicators of neurodevelopmental impairment.~~

~~To further describe the infant safety profile of retosiban, the following subgroups may be explored:~~

- ~~Gestational age of pregnancy at randomization~~
- ~~Established progesterone use (yes or no)~~
- ~~Magnesium sulfate use~~
- ~~Tocolytic use following study drug discontinuation~~
- ~~Maternal age~~
- ~~Region~~

~~For each subgroup, child safety data will be summarized by treatment and subgroup, as previously described.~~ Full details of all planned analyses will be provided in the RAP.

Section 8.3.5.2, Health Outcomes Analyses

The ~~primary~~ objective of the **exploratory** planned analysis ~~will be to use descriptive statistics~~ **is** to characterize resource utilization in infants exposed to retosiban or comparator in the Phase III SPTL treatment studies. ~~The~~ **Exploratory** endpoints ~~to be descriptively summarized~~ are those described in Section 6.3. Descriptive statistics ~~will~~ **may** be calculated by treatment group and by treatment group and time, where appropriate. ~~Additional analyses and modeling may be conducted to further characterize the resource utilization of infants exposed to retosiban, placebo, and atosiban.~~ Full details of the planned **exploratory** analyses will be provided in the RAP.

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

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

Section 9.5, Study and RCC Site Closure

Follow-up will continue until each child enrolled completes the ~~5-year questionnaire at 5 years chronological age.~~ **24-month questionnaire at 24 months chronological age. For any subject that was enrolled prior to Amendment 2, those subjects who have completed the 24 months assessments will not be required to complete the CHI questionnaire at 3, 4, and 5 years of the child's chronological age.**

Section 10, References

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