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

Summary

EudraCT number	2014-000499-24
Trial protocol	BE GB ES SE DE IT FR
Global end of trial date	02 September 2019

Results information

Result version number	v1
This version publication date	23 May 2020
First version publication date	23 May 2020

Trial information

Trial identification

Sponsor protocol code	200722

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001359-PIP01-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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 treatment studies.

Protection of trial subjects:

To minimize inconvenience to parents of the infants enrolled, this study did not require medical interventions or study visits to an investigational site. Instead, parents or legal guardians were prompted at certain timepoints to complete developmental questionnaires and other data regarding their child's health status via an electronic device.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Mexico: 22
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Israel: 32
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Japan: 6
Worldwide total number of subjects	98
EEA total number of subjects	22

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	4
Infants and toddlers (28 days-23 months)	94
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomized, long-term follow-up study to evaluate the safety and outcomes of infants and children born to women who received retosiban or comparator in the Phase III spontaneous preterm labor (SPTL) treatment studies:200719 (NCT02377466) and 200721 (NCT02292771). Current study was referred as a retosiban infant outcome study (ARIOS).

Pre-assignment

Screening details:

A total of 101 participants were screened and 98 participants were enrolled and randomized in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (200719 study)

Arm description:

All infants and children born to women who received the placebo (0.9 percent sodium chloride infusion matched for retosiban volume, intravenous [IV] loading dose over 5 minutes and continuous infusion rate including dose increase in participants with an inadequate response any time after first hour of treatment) in 200719 study. Current study did not require any medical interventions or study visits to an investigational site.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was available as 0.9 percent sodium chloride infusion matched for retosiban volume, intravenous (IV) loading dose over 5 minutes and continuous infusion rate including dose increase in participants with an inadequate response any time after first hour of treatment.

Arm title	Atosiban (200721 study)

Arm description:

All infants and children born to women who received atosiban (in 3 successive stages; an initial bolus dose of 6.75 milligram [mg] using atosiban 6.75 mg per 0.9 milliliter [mL] solution for injection, followed by continuous high dose infusion at 18 mg per hour for 3 hours, then a lower 6 mg per hour infusion for the remainder of the 48-hour using the atosiban 37.5 mg per 5 mL concentrate for solution) in 200721 study. Current study did not require any medical interventions or study visits to an investigational site.

Arm type	Active comparator
Investigational medicinal product name	Atosiban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atosiban was available as an initial bolus dose of 6.75 milligram (mg) using 6.75 mg per 0.9 milliliter

(mL) solution for injection, followed by continuous high dose infusion at 18 mg per hour for 3 hours, then a lower 6 mg per hour infusion for the remainder of the 48-hour using 37.5 mg per 5 mL concentrate for solution.

Arm title	Retosiban (200719 and 200721 study)

Arm description:

All infants and children born to women who received retosiban (6 mg IV loading dose of retosiban over 5 minutes followed by a 6 mg per hour continuous infusion of retosiban over 48 hours. Participants with an inadequate response any time after first hour of treatment were administered another 6 mg retosiban loading dose followed by 12 mg per hour continuous infusion for remainder of 48-hour treatment period) in 200719 study or 200721 study. Current study did not require any medical interventions or study visits to an investigational site.

Arm type	Experimental
Investigational medicinal product name	Retosiban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Retosiban was available as 6 mg IV loading dose over 5 minutes followed by a 6 milligram per hour continuous infusion of retosiban over 48 hours. Participants with an inadequate response any time after first hour of treatment were administered another 6 mg retosiban loading dose followed by 12 mg per hour continuous infusion for remainder of 48-hour treatment period

Number of subjects in period 1	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)
Started	5	44	49
Completed	4	24	28
Not completed	1	20	21
Consent withdrawn by subject	-	3	3
Lost to follow-up	1	17	18

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (200719 study)

Reporting group description:

All infants and children born to women who received the placebo (0.9 percent sodium chloride infusion matched for retosiban volume, intravenous [IV] loading dose over 5 minutes and continuous infusion rate including dose increase in participants with an inadequate response any time after first hour of treatment) in 200719 study. Current study did not require any medical interventions or study visits to an investigational site.

Reporting group title	Atosiban (200721 study)

Reporting group description:

All infants and children born to women who received atosiban (in 3 successive stages; an initial bolus dose of 6.75 milligram [mg] using atosiban 6.75 mg per 0.9 milliliter [mL] solution for injection, followed by continuous high dose infusion at 18 mg per hour for 3 hours, then a lower 6 mg per hour infusion for the remainder of the 48-hour using the atosiban 37.5 mg per 5 mL concentrate for solution) in 200721 study. Current study did not require any medical interventions or study visits to an investigational site.

Reporting group title	Retosiban (200719 and 200721 study)

Reporting group description:

All infants and children born to women who received retosiban (6 mg IV loading dose of retosiban over 5 minutes followed by a 6 mg per hour continuous infusion of retosiban over 48 hours. Participants with an inadequate response any time after first hour of treatment were administered another 6 mg retosiban loading dose followed by 12 mg per hour continuous infusion for remainder of 48-hour treatment period) in 200719 study or 200721 study. Current study did not require any medical interventions or study visits to an investigational site.

Reporting group values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)
Number of subjects	5	44	49
Age categorical Units: Subjects			
Total Participants	5	44	49
Age Continuous Units: Months			
arithmetic mean	2.16	2.18	2.12
standard deviation	± 1.479	± 1.158	± 0.932
Sex: Female, Male Units: Participants			
Female	1	18	21
Male	4	26	28
Race/Ethnicity, Customized Units: Subjects			
African American/African (Afr) Heritage	0	1	1
American Indian or Alaskan Native	0	5	6
Asian-Central/South Asian Heritage	0	0	1
Asian-East Asian Heritage	1	4	8
Asian-Japanese Heritage	4	0	2
White-Arabic/North Afr/Caucasian/European Heritage	0	34	31

Reporting group values	Total		
Number of subjects	98		

Age categorical Units: Subjects			
Total Participants	98		
Age Continuous Units: Months arithmetic mean standard deviation	 -		
Sex: Female, Male Units: Participants			
Female	40		
Male	58		
Race/Ethnicity, Customized Units: Subjects			
African American/African (Afr) Heritage	2		
American Indian or Alaskan Native	11		
Asian-Central/South Asian Heritage	1		
Asian-East Asian Heritage	13		
Asian-Japanese Heritage	6		
White-Arabic/North Afr/Caucasian/European Heritage	65		

End points

End points reporting groups

Reporting group title	Placebo (200719 study)

Reporting group description:

All infants and children born to women who received the placebo (0.9 percent sodium chloride infusion matched for retosiban volume, intravenous [IV] loading dose over 5 minutes and continuous infusion rate including dose increase in participants with an inadequate response any time after first hour of treatment) in 200719 study. Current study did not require any medical interventions or study visits to an investigational site.

Reporting group title	Atosiban (200721 study)

Reporting group description:

All infants and children born to women who received atosiban (in 3 successive stages; an initial bolus dose of 6.75 milligram [mg] using atosiban 6.75 mg per 0.9 milliliter [mL] solution for injection, followed by continuous high dose infusion at 18 mg per hour for 3 hours, then a lower 6 mg per hour infusion for the remainder of the 48-hour using the atosiban 37.5 mg per 5 mL concentrate for solution) in 200721 study. Current study did not require any medical interventions or study visits to an investigational site.

Reporting group title	Retosiban (200719 and 200721 study)

Reporting group description:

All infants and children born to women who received retosiban (6 mg IV loading dose of retosiban over 5 minutes followed by a 6 mg per hour continuous infusion of retosiban over 48 hours. Participants with an inadequate response any time after first hour of treatment were administered another 6 mg retosiban loading dose followed by 12 mg per hour continuous infusion for remainder of 48-hour treatment period) in 200719 study or 200721 study. Current study did not require any medical interventions or study visits to an investigational site.

Primary: Number of infants and children with newly diagnosed chronic medical conditions (after 28 days post estimated date of delivery)

End point title	Number of infants and children with newly diagnosed chronic medical conditions (after 28 days post estimated date of delivery)[1]

End point description:

The parents of the infants filled in an online child health inventory (CHI) questionnaire, which asked them about each condition. If they reported anything, it was then verified by a healthcare professional. ARIOS Safety Population was a subset of the Infant Safety Population (all the infants whose mothers were randomized and received retosiban or comparator in any of the Phase III treatment trials) for which the mother/infant pairs were enrolled into the ARIOS study. Number of infants and children with newly diagnosed chronic medical conditions are presented.

End point type	Primary

End point timeframe:

From 28 days post estimated date of delivery up to 24 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[2]	44[3]	49[4]	
Units: Participants	0	1	3	

Notes:

[2] - ARIOS Safety Population

[3] - ARIOS Safety Population

[4] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants and children with newly diagnosed congenital anomalies (after 28 days post estimated date of delivery)

End point title	Number of infants and children with newly diagnosed congenital anomalies (after 28 days post estimated date of delivery)[5]

End point description:

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. Congenital anomaly serious adverse events (SAEs) were examined by the birth defect evaluator. Events were coded per centers for disease control and prevention (CDC) Metropolitan Atlanta congenital defects program (MACDP) criteria and/or European surveillance of congenital anomalies (EUROCAT) criteria. Predefined defect codes specified whether the defect was face and neck, a cleft lip or palate, cardiovascular, respiratory, upper gastrointestinal, female genitalia, male genitalia, renal and urinary system, other musculoskeletal defects, skin, a chromosome anomaly, other organ systems, or a specified syndrome. Number of infants and children with newly diagnosed congenital anomalies reported up to 1 year of chronological age and reported after 1 year of chronological age are presented.

End point type	Primary

End point timeframe:

From 28 days post estimated date of delivery up to 24 months

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[6]	44[7]	49[8]	
Units: Participants				
Up to 1 year of chronological age	0	0	2	
After 1 year of chronological age	0	0	0	

Notes:

[6] - ARIOS Safety Population

[7] - ARIOS Safety Population

[8] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infant and child death (after 28 days post estimated date of delivery)

End point title	Number of infant and child death (after 28 days post estimated date of delivery)[9]

End point description:

Number of infant and child death that occurred after 28 days post estimated date of delivery and up to 24 months are presented.

End point type	Primary

End point timeframe:

From 28 days post estimated date of delivery up to 24 months

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[10]	44[11]	49[12]	
Units: Participants	0	0	0	

Notes:

[10] - ARIOS Safety Population

[11] - ARIOS Safety Population

[12] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for any domain at 9 months

End point title	Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for any domain at 9 months[13]

End point description:

The ASQ-3 included 6 questions in each area, designed to assess: communication skills, gross motor skills, fine motor skills, problem solving skills, and personal social skills. Parents answered either yes(10 points), sometimes(5 points) or not yet(0 points) to each question to complete ASQ-3. At 9 months, the pre-defined cut-off score for communication was 13.97,gross motor was 17.82,fine motor was 31.32, problem solving was 28.72 and personal social skills was 18.91. Total score was derived by taking mean of all 5 components. Any infant who scored below the cut-off,a score more than or equal to 2 standard deviations below the mean score (that is Black zone in the score chart) in any of the 5 areas of the ASQ-3 was to be referred to a developmental specialist for a formal neurodevelopmental assessment. Number of infants with ASQ-3 scores for any domains in the black zone at 9 months is presented. Only those participants with data available at the specified data points were analyzed.

End point type	Primary

End point timeframe:

At 9 months

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[14]	17[15]	20[16]	
Units: Participants	0	4	4	

Notes:

[14] - ARIOS Safety Population

[15] - ARIOS Safety Population

[16] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for any domain at 18 months

End point title	Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for any domain at 18 months[17]

End point description:

The ASQ-3 included 6 questions in each area, designed to assess: communication skills, gross motor skills, fine motor skills, problem solving skills, and personal social skills. Parents answered either yes(10 points), sometimes(5 points) or not yet(0 points) to each question to complete ASQ-3. At 18 months, the pre-defined cut-off score for communication was 13.06,gross motor was 37.38,fine motor was 34.32, problem solving was 25.74 and personal social skills was 27.19. Total score was derived by taking mean of all 5 components. Any infant who scored below the cut-off,a score more than or equal to 2 standard deviations below the mean score(that is Black zone in the score chart)in any of the 5 areas of the ASQ-3 was to be referred to a developmental specialist for a formal neurodevelopmental assessment. Number of infants with ASQ-3 scores for any domains in the black zone at 18 months is presented. Only those participants with data available at the specified data points were analyzed.

End point type	Primary

End point timeframe:

At 18 months

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[18]	19[19]	18[20]	
Units: Participants	2	5	0	

Notes:

[18] - ARIOS Safety Population

[19] - ARIOS Safety Population

[20] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for any domain at 24 months

End point title	Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for any domain at 24 months[21]

End point description:

The ASQ-3 included 6 questions in each area, designed to assess: communication skills, gross motor skills, fine motor skills, problem solving skills, and personal social skills. Parents answered either yes(10 points), sometimes(5 points) or not yet(0 points) to each question to complete ASQ-3. At 24 months, the pre-defined cut-off score for communication was 25.17,gross motor was 38.07,fine motor was

35.16, problem solving was 29.78 and personal social skills was 31.54. Total score was derived by taking mean of all 5 components. Any infant who scored below the cut-off, a score more than or equal to 2 standard deviations below the mean score(that is Black zone in the score chart)in any of the 5 areas of the ASQ-3 was to be referred to a developmental specialist for a formal neurodevelopmental assessment. Number of infants with ASQ-3 scores for any domains in the black zone at 24 months is presented. Only those participants with data available at the specified data points were analyzed

End point type	Primary

End point timeframe:

At 24 months

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[22]	19[23]	25[24]	
Units: Participants	1	2	2	

Notes:

[22] - ARIOS Safety Population

[23] - ARIOS Safety Population

[24] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for gross motor skills

End point title	Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for gross motor skills[25]

End point description:

The ASQ-3 included 6 questions in each area; communication skills, gross motor skills, fine motor skills, problem solving skills, and personal social skills. Parents answered either yes (10 points), sometimes (5 points) or not yet (0 points) to each question to complete ASQ-3. At 9 months, the pre-defined cut-off score for gross motor skills was 17.82. At 18 months, it was 37.38. At 24 months, it was 38.07. Any infant who scored below the cut-off, a score more than or equal to 2 standard deviations below the mean score (that is Black zone in the score chart) in any of the 5 areas of the ASQ-3 was to be referred to a developmental specialist. Number of infants with ASQ-3 scores for gross motor skills in the black zone at 9, 18 and 24 months is presented. All 98 participants in the study were included in the analysis (5, 44 and 49 Participants), but only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

9, 18 and 24 months

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[26]	44[27]	49[28]	
Units: Participants				
9 months, n=3,17,20	0	1	0	
18 months, n=3,19,18	1	1	0	
24 months, n=2,19,25	0	1	0	

Notes:

[26] - ARIOS Safety Population

[27] - ARIOS Safety Population

[28] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for fine motor skills

End point title	Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for fine motor skills[29]

End point description:

The ASQ-3 included 6 questions in each area; communication skills, gross motor skills, fine motor skills, problem solving skills, and personal social skills. Parents answered either yes (10 points), sometimes (5 points) or not yet (0 points) to each question to complete ASQ-3. At 9 months, the pre-defined cut-off score for fine motor skills was 31.32. At 18 months, it was 34.32. At 24 months, it was 35.16. Any infant who scored below the cut-off, a score more than or equal to 2 standard deviations below the mean score (that is Black zone in the score chart) in any of the 5 areas of the ASQ-3 was to be referred to a developmental specialist. Number of infants with ASQ-3 scores for fine motor skills in the black zone at 9, 18 and 24 months is presented. All 98 participants in the study were included in the analysis (5, 44 and 49 Participants), but only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

9, 18 and 24 months

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[30]	44[31]	49[32]	
Units: Participants				
9 months, n=3,17,20	0	0	2	
18 months, n=3,19,18	1	2	0	
24 months, n=2,19,25	0	0	0	

Notes:

[30] - ARIOS Safety Population

[31] - ARIOS Safety Population

[32] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for communication skills

End point title	Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for communication skills[33]

End point description:

The ASQ-3 included 6 questions in each area; communication skills, gross motor skills, fine motor skills, problem solving skills, and personal social skills. Parents answered either yes (10 points), sometimes (5 points) or not yet (0 points) to each question to complete ASQ-3. At 9 months, the pre-defined cut-off score for communication skills was 13.97. At 18 months, it was 13.06. At 24 months, it was 25.17. Any infant who scored below the cut-off, a score more than or equal to 2 standard deviations below the mean score (that is Black zone in the score chart) in any of the 5 areas of the ASQ-3 was to be referred to a developmental specialist. Number of infants with ASQ-3 scores for communication skills in the black zone at 9, 18 and 24 months is presented. All 98 participants in the study were included in the analysis (5, 44 and 49 Participants), but only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

9, 18 and 24 months

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[34]	44[35]	49[36]	
Units: Participants				
9 months, n=3,17,20	0	1	1	
18 months, n=3,19,18	1	0	0	
24 months, n=2,19,25	1	1	2	

Notes:

[34] - ARIOS Safety Population

[35] - ARIOS Safety Population

[36] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for problem solving skills

End point title	Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for problem solving skills[37]

End point description:

The ASQ-3 included 6 questions in each area; communication skills, gross motor skills, fine motor skills, problem solving skills, and personal social skills. Parents answered either yes (10 points), sometimes (5 points) or not yet (0 points) to each question to complete ASQ-3. At 9 months, the pre-defined cut-off score for problem solving skills was 28.72. At 18 months, it was 25.74. At 24 months, it was 29.78. Any infant who scored below the cut-off, a score more than or equal to 2 standard deviations below the mean score (that is Black zone in the score chart) in any of the 5 areas of the ASQ-3 was to be referred to a developmental specialist. Number of infants with ASQ-3 scores for problem solving skills in the black zone at 9, 18 and 24 months is presented. All 98 participants in the study were included in the analysis (5, 44 and 49 Participants),but only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

9, 18 and 24 months

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[38]	44[39]	49[40]	
Units: Participants				
9 months, n=3,17,20	0	1	2	
18 months, n=3,19,18	0	1	0	
24 months, n=2,19,25	0	1	0	

Notes:

[38] - ARIOS Safety Population

[39] - ARIOS Safety Population

[40] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for personal social skills

End point title	Number of infants with ages and stages questionnaire-3 (ASQ-3) score in the black zone for personal social skills[41]

End point description:

The ASQ-3 included 6 questions in each area; communication skills, gross motor skills, fine motor skills, problem solving skills, and personal social skills. Parents answered either yes (10 points), sometimes (5 points) or not yet (0 points) to each question to complete ASQ-3. At 9 months, the pre-defined cut-off score for personal social skills was 18.91. At 18 months, it was 27.19. At 24 months, it was 31.54. Any infant who scored below the cut-off, a score more than or equal to 2 standard deviations below the mean score (that is Black zone in the score chart) in any of the 5 areas of the ASQ-3 was to be referred to a developmental specialist. Number of infants with ASQ-3 scores for personal social skills in the black zone at 9, 18 and 24 months is presented. All 98 participants in the study were included in the analysis (5, 44 and 49 Participants),but only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

9, 18 and 24 months

Notes:

[41] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[42]	44[43]	49[44]	
Units: Participants				
9 months, n=3,17,20	0	2	0	
18 months, n=3,19,18	0	1	0	

24 months, n=2,19,25	0	1	0	

Notes:

[42] - ARIOS Safety Population

[43] - ARIOS Safety Population

[44] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants referred for developmental evaluation using Bayley scales of infant development, third edition (BSID-III)

End point title	Number of infants referred for developmental evaluation using Bayley scales of infant development, third edition (BSID-III)[45]

End point description:

Any infant who scored below the cut-off i.e., a score greater than or equal to 2 Standard Deviations (SDs) below the mean score (i.e., black zone in the score chart) in any of the 5 domains of the ASQ-3 was evaluated using the BSID-III. It scaled scores for cognitive, language (receptive and expressive), motor (fine and gross motor). The language and motor areas each have a composite score, with a mean of 100, a SD of 15 and a range of 40 to 160. Scores lower than 70 indicated moderate or severe impairment. In the cognitive area, the infant scored "1" if they could do an activity and "0" if they could not. Total score was derived by taking mean of all the components. Number of infants referred for developmental evaluation using BSID-III is presented. All 98 participants in the study were included in the analysis (5, 44 and 49 Participants), but only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

9, 18 and 24 months

Notes:

[45] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[46]	44[47]	49[48]	
Units: Participants				
9 months, n=0,4,4	0	1	3	
18 months, n=2,5,0	2	3	0	
24 months, n=1,2,2	0	2	1	

Notes:

[46] - ARIOS Safety Population

[47] - ARIOS Safety Population

[48] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with Bayley Scales of Infant Development, third edition score greater than 2 standard deviation below the mean score for the cognitive scale (less than 4)

End point title	Number of infants with Bayley Scales of Infant Development, third edition score greater than 2 standard deviation below the

	mean score for the cognitive scale (less than 4)[49]

End point description:

Any infant who scored below the cut-off i.e., a score greater than or equal to 2 Standard Deviations (SDs) below the mean score (i.e., black zone in the score chart) in any of the 5 domains of the ASQ-3 was evaluated using the BSID-III. It scaled scores for cognitive, language (receptive and expressive), motor (fine and gross motor). The language and motor areas each have a composite score, with a mean of 100, a SD of 15 and a range of 40 to 160. Scores lower than 70 indicated moderate or severe impairment. In the cognitive area, the infant scored "1" if they could do an activity and "0" if they could not. Number of infants with BSID-III score greater than 2 SD below the mean score for the cognitive scale (less than 4) is presented. All 98 participants in the study were included in the analysis (5, 44 and 49 Participants), but only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

9, 18 and 24 months

Notes:

[49] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[50]	44[51]	49[52]	
Units: Participants				
9 months, n=0,0,1	0	0	0	
18 months, n=0,2,0	0	2	0	
24 months, n=0,0,1	0	0	1	

Notes:

[50] - ARIOS Safety Population

[51] - ARIOS Safety Population

[52] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with Bayley Scales of Infant Development, third edition score greater than 2 standard deviation below the mean score for the gross motor scale (less than 4)

End point title	Number of infants with Bayley Scales of Infant Development, third edition score greater than 2 standard deviation below the mean score for the gross motor scale (less than 4)[53]

End point description:

Any infant who scored below the cut-off i.e., a score greater than or equal to 2 Standard Deviations (SDs) below the mean score (i.e., black zone in the score chart) in any of the 5 domains of the ASQ-3 was evaluated using the BSID-III. It scaled scores for cognitive, language (receptive and expressive), motor (fine and gross motor). The language and motor areas each have a composite score, with a mean of 100, a SD of 15 and a range of 40 to 160. Scores lower than 70 indicated moderate or severe impairment. In the cognitive area, the infant scored "1" if they could do an activity and "0" if they could not. Number of infants with BSID-III score greater than 2 SD below the mean score for the gross motor scale (less than 4) is presented. All 98 participants in the study were included in the analysis (5, 44 and 49 Participants), but only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

9, 18 and 24 months

Notes:

[53] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[54]	44[55]	49[56]	
Units: Participants				
9 months, n=0,0,1	0	0	0	
18 months, n=0,2,0	0	2	0	
24 months, n=0,0,1	0	0	1	

Notes:

[54] - ARIOS Safety Population

[55] - ARIOS Safety Population

[56] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with Bayley Scales of Infant Development, third edition score greater than 2 standard deviation below the mean score for the fine motor scale (less than 4)

End point title	Number of infants with Bayley Scales of Infant Development, third edition score greater than 2 standard deviation below the mean score for the fine motor scale (less than 4)[57]

End point description:

Any infant who scored below the cut-off i.e., a score greater than or equal to 2 Standard Deviations (SDs) below the mean score (i.e., black zone in the score chart) in any of the 5 domains of the ASQ-3 was evaluated using the BSID-III. It scaled scores for cognitive, language (receptive and expressive), motor (fine and gross motor). The language and motor areas each have a composite score, with a mean of 100, a SD of 15 and a range of 40 to 160. Scores lower than 70 indicated moderate or severe impairment. In the cognitive area, the infant scored "1" if they could do an activity and "0" if they could not. Number of infants with BSID-III score greater than 2 SD below the mean score for the fine motor scale (less than 4) is presented. All 98 participants in the study were included in the analysis (5, 44 and 49 Participants), but only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

9, 18 and 24 months

Notes:

[57] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[58]	44[59]	49[60]	
Units: Participants				
9 months, n=0,0,1	0	0	0	
18 months, n=0,2,0	0	2	0	
24 months, n=0,0,1	0	0	1	

Notes:

[58] - ARIOS Safety Population

[59] - ARIOS Safety Population

[60] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with Bayley Scales of Infant Development, third edition score greater than 2 standard deviation below the mean score for the language scale (less than 70)

End point title	Number of infants with Bayley Scales of Infant Development, third edition score greater than 2 standard deviation below the mean score for the language scale (less than 70)[61]

End point description:

Any infant who scored below the cut-off i.e., a score greater than or equal to 2 Standard Deviations (SDs) below the mean score (i.e., black zone in the score chart) in any of the 5 domains of the ASQ-3 was evaluated using the BSID-III. It scaled scores for cognitive, language (receptive and expressive), motor (fine and gross motor). The language and motor areas each have a composite score, with a mean of 100, a SD of 15 and a range of 40 to 160. Scores lower than 70 indicated moderate or severe impairment. In the cognitive area, the infant scored "1" if they could do an activity and "0" if they could not. Number of infants with BSID-III score greater than 2 SD below the mean score for the language scale (less than 70) is presented. All 98 participants in the study were included in the analysis (5, 44 and 49 Participants), but only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

9, 18 and 24 months

Notes:

[61] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[62]	44[63]	49[64]	
Units: Participants				
9 months, n=0,0,1	0	0	0	
18 months, n=0,2,0	0	2	0	
24 months, n=0,0,1	0	0	1	

Notes:

[62] - ARIOS Safety Population

[63] - ARIOS Safety Population

[64] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with a child behavior checklist for ages 1.5 to 5 years (CBCL/1.5 to 5) score above the 97th percentile for a subset of prespecified questions that relate to attention and hyperactivity problems

End point title	Number of infants with a child behavior checklist for ages 1.5 to 5 years (CBCL/1.5 to 5) score above the 97th percentile for a subset of prespecified questions that relate to attention and hyperactivity problems[65]

End point description:

The CBCL/1.5 to 5 questionnaire is a parent-completed questionnaire used for assessing behavioral and social competencies. It included approximately 100 items that characterized preschool children between the ages of 1.5 and 5 years. Each question could be answered as "not true scored as"0",somewhat or sometimes true scored as"1"or very true or often true scored as "2". There were 6 questions related to attention and hyperactivity problems. The responses to those 6 questions were summed (ranged 0 to 12). Total score of 0 to 9 indicated normal,10 indicated borderline and 11 to 12 indicated significant attention and hyperactivity problems. Scores above the 97th percentile are in the significant range of clinical concern. Number of infants with CBCL/1.5 to 5 score above 97th percentile for subset of pre-specified questions related to attention and hyperactivity problems at 24 months is reported. Only those participants with data available at the specified data points were analyzed.

End point type	Primary

End point timeframe:

At 24 months

Notes:

[65] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[66]	12[67]	14[68]	
Units: Participants	0	1	0	

Notes:

[66] - ARIOS Safety Population

[67] - ARIOS Safety Population

[68] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants indicated as needing further evaluation after completion of the modified checklist for autism in toddlers- revised with follow-up (M-CHAT-R/F)

End point title	Number of infants indicated as needing further evaluation after completion of the modified checklist for autism in toddlers-revised with follow-up (M-CHAT-R/F)[69]

End point description:

The M-CHAT-R/F is a parent-reported autism screening tool designed to identify children 16 to 30 months of age who received a more thorough assessment for possible early signs of autism spectrum disorder (ASD) or developmental delay. The M-CHAT-R/F consisted of 20 questions that were answered with either "yes, scored as 0" or "no, scored as 1". Total scores (ranged 0 to 20) on the M-CHAT-R/F between 0 and 2 indicated a low risk, scores between 3 and 7 indicated a medium risk and triggered administration of the follow-up questionnaire, and scores between 8 and 20 indicated a high risk. Number of infants who needed further evaluation as per the M-CHAT-R/F at 18 and 24 months is presented. All 98 participants in the study were included in the analysis (5, 44 and 49 Participants), but only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

18 and 24 months

Notes:

[69] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[70]	44[71]	49[72]	
Units: Participants				
18 months,n=2,10,7	0	0	0	
24 months,n=2,11,13	0	0	0	

Notes:

[70] - ARIOS Safety Population

[71] - ARIOS Safety Population

[72] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants referred for neurological evaluation to determine diagnosis of cerebral palsy

End point title	Number of infants referred for neurological evaluation to determine diagnosis of cerebral palsy[73]

End point description:

Parents reported in CHI questionnaire if their infant had cerebral palsy. If the infant was not diagnosed with cerebral palsy, then this was detected as part of the ASQ-3 assessment, based on the results of the gross motor scale. To confirm the diagnosis of cerebral palsy, the healthcare practitioner referred the infant for further neurological tests if they scored in the black zone of the ASQ-3 at the month 24 assessment. Number of infants referred for neurological evaluation to determine diagnosis of cerebral palsy at 24 months is presented. Only those participants with data available at the specified data points were analyzed.

End point type	Primary

End point timeframe:

At 24 months

Notes:

[73] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[74]	19[75]	25[76]	
Units: Participants	0	0	0	

Notes:

[74] - ARIOS Safety Population

[75] - ARIOS Safety Population

[76] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of infants with the indicators of neurodevelopmental impairment

End point title	Number of infants with the indicators of neurodevelopmental impairment[77]

End point description:

The indicators of neurodevelopmental impairment were 'hearing impaired, uncorrected even with aids'; 'blindness in 1 or both eyes, or sees light only'; 'cerebral palsy-moderate and severe (moderate: Grade 2 or 3 using the gross motor functional classification system [GMFCS] and severe: Grade 4 or 5 using the GMFCS)'; 'cognitive impairment: BSID-III cognitive scale score of less than 2 SDs below mean score (less than 4)'; 'motor impairment: BSID-III motor composite scale score of greater than 2 SDs below mean score (less than 70)'; 'diagnosis of ASD, attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD)'. Number of infants having any 1 of these indicators is presented. Only those participants with data available at the specified data points were analyzed.

End point type	Primary

End point timeframe:

Up to 24 months

Notes:

[77] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Placebo (200719 study)	Atosiban (200721 study)	Retosiban (200719 and 200721 study)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[78]	30[79]	36[80]	
Units: Participants				
Hearing impaired, uncorrected even with aids	0	0	0	
Blindness in 1 or both eyes, or sees light only	0	0	0	
Cerebral palsy (moderate and severe)	0	0	0	
Cognitive impairment	0	1	1	
Motor impairment	0	1	1	
Diagnosis of ASD,ADD or ADHD	0	1	0	

Notes:

[78] - ARIOS Safety Population

[79] - ARIOS Safety Population

[80] - ARIOS Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Serious adverse events (SAEs) were collected for infants from after 28 days post estimated due date until maximum of 24 months chronological age. Non-SAEs were not collected, since all the adverse events that occurred in infants were considered as SAEs

Adverse event reporting additional description:

SAEs were reported for ARIOS Safety Population which comprised of a subset of Infant Safety Population (all the infants whose mothers were randomized and received retosiban or comparator in any of the Phase III treatment trials) for which the mother/infant pairs were enrolled into the ARIOS study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo (200719 study)

Reporting group description:

All infants and children born to women who received the placebo (0.9 percent sodium chloride infusion matched for retosiban volume, intravenous [IV] loading dose over 5 minutes and continuous infusion rate including dose increase in participants with an inadequate response any time after first hour of treatment) in 200719 study. Current study did not require any medical interventions or study visits to an investigational site.

Reporting group title	Retosiban (200719 and 200721 study)

Reporting group description:

All infants and children born to women who received retosiban (6 mg IV loading dose of retosiban over 5 minutes followed by a 6 mg per hour continuous infusion of retosiban over 48 hours. Participants with an inadequate response any time after first hour of treatment were administered another 6 mg retosiban loading dose followed by 12 mg per hour continuous infusion for remainder of 48-hour treatment period) in 200719 study or 200721 study. Current study did not require any medical interventions or study visits to an investigational site.

Reporting group title	Atosiban (200721 study)

Reporting group description:

All infants and children born to women who received atosiban (in 3 successive stages; an initial bolus dose of 6.75 milligram [mg] using atosiban 6.75 mg per 0.9 milliliter [mL] solution for injection, followed by continuous high dose infusion at 18 mg per hour for 3 hours, then a lower 6 mg per hour infusion for the remainder of the 48-hour using the atosiban 37.5 mg per 5 mL concentrate for solution) in 200721 study. Current study did not require any medical interventions or study visits to an investigational site.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Non-SAEs were not collected, since all the adverse events that occurred in infants were considered as SAEs

Serious adverse events	Placebo (200719 study)	Retosiban (200719 and 200721 study)	Atosiban (200721 study)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	3 / 49 (6.12%)	6 / 44 (13.64%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Injury of genitals			

subjects affected / exposed	0 / 5 (0.00%)	1 / 49 (2.04%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital cataract			
subjects affected / exposed	0 / 5 (0.00%)	1 / 49 (2.04%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital hydrocoele			
subjects affected / exposed	0 / 5 (0.00%)	1 / 49 (2.04%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Circumoral cyanosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 49 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Cervical lymphadenitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 49 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	0 / 5 (0.00%)	1 / 49 (2.04%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 49 (2.04%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 5 (0.00%)	1 / 49 (2.04%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute bronchiolitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 49 (2.04%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract			
subjects affected / exposed	0 / 5 (0.00%)	1 / 49 (2.04%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 49 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 49 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 49 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo (200719 study)	Retosiban (200719 and 200721 study)	Atosiban (200721 study)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 49 (0.00%)	0 / 44 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2015	Amendment 01: Extended the study duration from 24 months to 5 years; added an assessment using a modified version of the child health inventory questionaire; added an additional assessment of modified checklist for autism in toddlers-revised with follow-up (M-CHAT-R/F); revised child behavior checklist (CBCl/1.5 to 5) per American academy of pediatrics guidelines, deletion of neurodevelopment endpoint for an additional behaviour assessment using M-CHAT-R/F and CBCl/1.5 to 5; revised the subgroups to reflect study design of Phase III spontaneous preterm labour Study 200719 (NEWBORN-1); clarified unblinding text; incorporation of other administrative changes
01 November 2018	Amendment 02: Reduction of study duration from 5 years to 24 months; termination of retosiban development program; low recruitment for 200719 (NEWBORN-1) and 200721 (ZINN) studies; modification in the recommendation of independent data monitoring committee; reclassification of all resource utilization endpoints as exploratory endpoints due to the reduced sample size; correction of an error in the mean Bayley Scales of Infant Development, third edition (BSID-III) score; incorporation of other administrative changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported